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TOWARDS THE SYNTHESIS OF SCYPHOSTATIN

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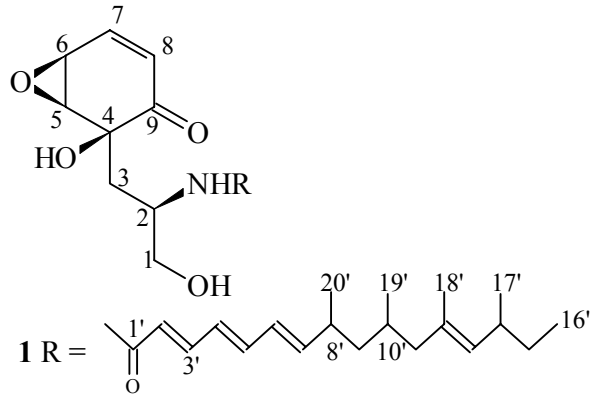
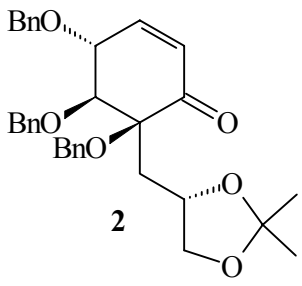
Abstract - Stereocontrolled synthesis of the substituted cyclohexenone segment (**2**) of scyph-ostatin (**1**) is described starting from D-glucose.

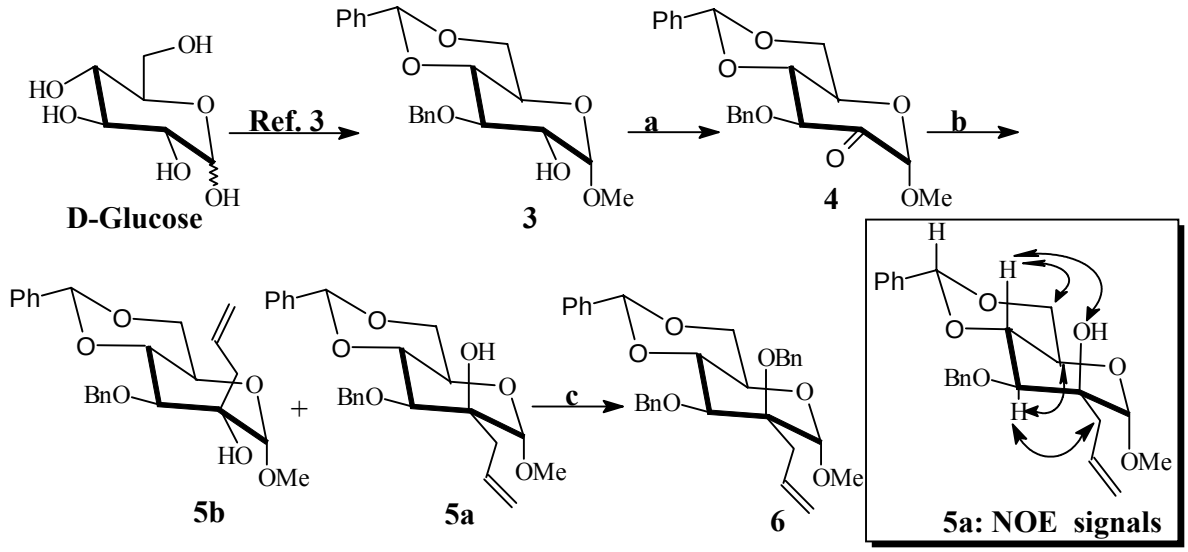
Scyphostatin (**1**) is a novel neutral sphingomyelinase (N-Smase) inhibitor isolated[1] during the search for N-Smase inhibitors from the fermentation broth of *Dascysphus mollissimus* SANK-13892. N-Smase inhibitors are useful in the regulation of ceramide level and thus are of immense need in the therapy of autoimmune diseases and inflammation.[2] Scyphostatin (**1**) is a structurally unique natural product containing an unprecedented cyclohexenone epoxide moiety in which the *tertiary* chiral center at C-4 is linked to an *n*-propylamino alcohol and a lipophilic side chain[C(1′)-C(20′)]. The structure of scyphostatin (**1**) was determined by NMR and MS spectral studies. Chemical and spectroscopic analysis, coupled with modified Mosher's method, provided stereo-





chemical configuration of the cyclohexenone epoxide ring structure of scyphostatin. However, the initial report[1] did not confirm the absolute configuration of the lipophilic side chain. Later Saito *et al.* has confirmed[3] the absolute and relative configurations by degradation of **1** and chemical correlation to synthetic fragments. Hoye *et al.*[4] have synthesized the lipophilic side chain and till date there is no single report on synthesis of polar cyclohexenone moiety. As part of our interest, we have embarked on developing a carbohydrate based strategy to prepare the suitably substituted cyclohexenone derivative (**2**) present in the scyphostatin (**1**). D-Glucose was converted[5] into methyl 3-*O*-benzyl-4,6-benzylidene-α-D-glucopyranoside (**3**) whose oxidation at C-2 under

Swern conditions, gave the 2-ulose derivative (**4**) (Scheme 1).[6] Subsequent *C*-allylation of **4** was studied[7] under various conditions. However, we observed that **4** with allylmagnesium bromide in anhydrous ether/CH_2Cl_2 at –78 ^oC gave a 9:1 diastereomeric mixture of *tertiary* alcohols (**5a**) and (**5b**) which were separated by silica gel column chromatography. The major product was subjected to NOE studies which unequivocally proved the structure as **5a** while the structure of the minor product (**5b**) was unambiguously assigned based on interesting chemical transformations.[7b]

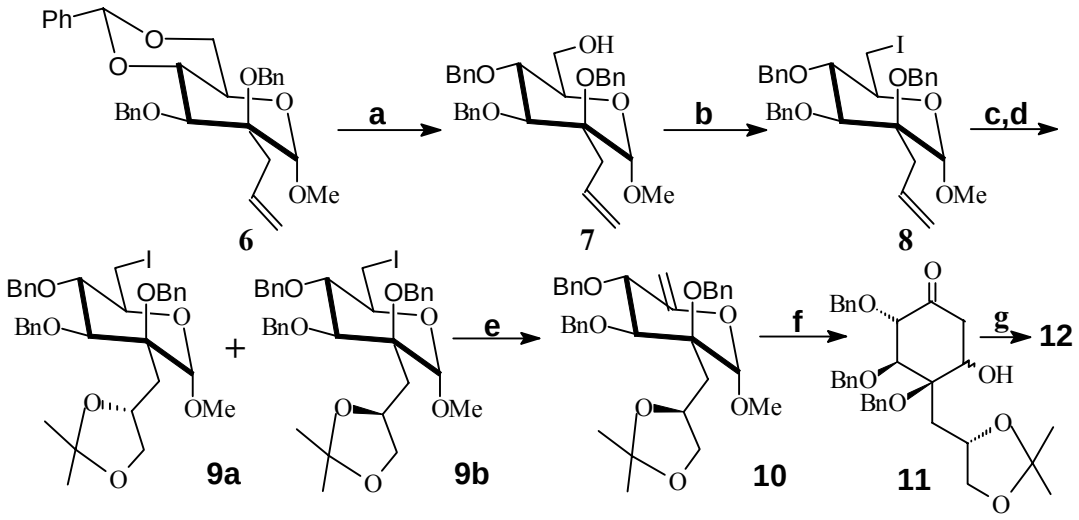


Scheme 1: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC, 89 %; b) allylmagnesium bromide, Et_2O:CH_2Cl_2 (4:1), -78 ^oC, 68 %; c) NaH, BnBr, DMF, n-Bu_4NI, , 0 ^oC-rt, 97 %.

The derived *O*-benzyl derivative (**6**) was reduced[8] with $LiAlH_4$-$AlCl_3$ to give rise to the 4-*O*-benzyl derivative (**7**) containing a primary hydroxy group at C-6. Treatment of **7** with Ph_3P-I_2-imidazole in toluene gave[9] the 6-deoxy-6-iodo derivative (**8**) (Scheme **2**). Catalytic osmylation of **8** in *t*-butanol-water gave a 4:1 mixture of diastereomeric products whose acetonide derivatives (**9a/9b)** could be separated by silica gel column chromatography. In accordance with Sharpless modifications,[10] use of AD-MIX-α provided predominantly the diastereomer (**9b)** whose stereochemical assignments were based on hypothesis reported by Sharpless *et al* .[10] Compound (**9b)** was treated with DBU in DMF at 100^oC for 12 h to give the 5,6-ene derivative (**10**). The Ferrier rearrangement[11] of **10** in the presence of $Hg(OAc)_2$ in aqueous acetone gave the carbocyclic derivative (**11**) whose dehydration in the presence of MsCl-Et_3N-CH_2Cl_2 provided the α, β-unsaturated derivative (**12**) (Scheme 3). In order to rearrange **12**, into the target structure (**2**), an approach based on Barton's radical opening reaction[12] of α,β-epoxythioimidazolide was investigated (Scheme 3).

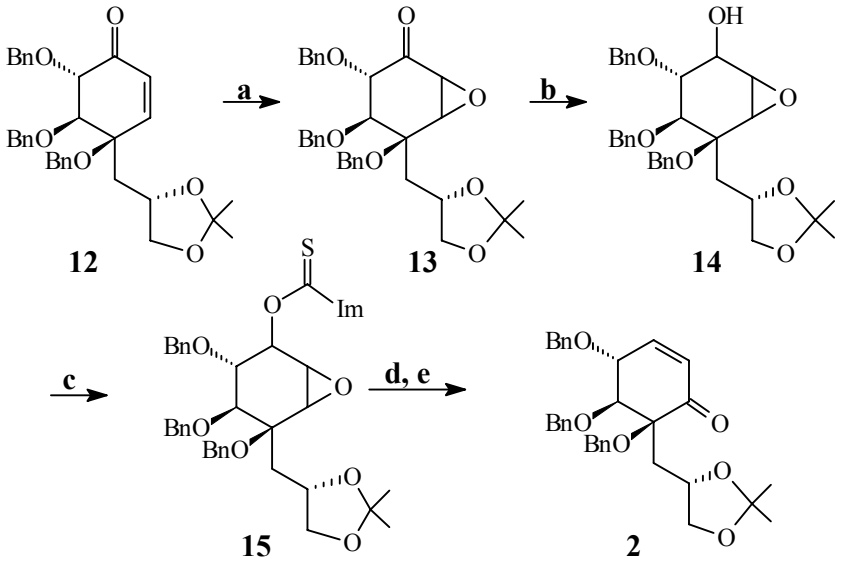
Compound (**12**) was epoxidised with 30 % hydrogen peroxide-K_2CO_3 in THF-H_2O to give **13** which was consequently reduced with $NaBH_4$ in methanol to give the epoxy alcohol (**14**). In the ^{1}H-NMR spectrum of **14,** epoxy protons were clearly visible at 3.23 (doublet, J = 3.8 Hz) and 3.35 ppm (triplet, J = 3.8 Hz). Conversion of **14** into the thiocarbonate derivative (**15**) was accomplished with *N,N'*-thiocarbonyldiimidazole in

refluxing C_6H_6. The ^{1}H-NMR spectrum of **15** showed characteristic downfield shift of the proton carrying



Scheme 2: a) $LiAlH_4$, $AlCl_3$, Et_2O, 15 min, 90 %; b) PPh_3, Im, I_2, C_6H_5Me, reflux, 2 h, 95 %; c) AD-mix-α, *t*-BuOH-H_2O (1:1), 0 °C, 24 h, 89 %; d) DMP, PTSA, CH_2Cl_2, rt, 30 min, 98 %; e) DBU, DMF, 100 °C, 12 h, 48 %; f) $Hg(OAc)_2$, MeCOMe, H_2O (3:1), reflux, 5 h, 80 %;g) MsCl, Et_3N, CH_2Cl_2, rt, 3 h, 85 %

thiocarbonate group. Treatment of **15** with Bu_3SnH and cat. AIBN in refluxing benzene gave a mixture of products from which the major product was isolated (30 %) by silica gel chromatography. Subsequent oxidation with MnO_2 in refluxing CH_2Cl_2 provided the target cyclohexenone derivative (**2**). In the ^{1}H-NMR spectrum of **2**, the characteristic[13] signals due to olefinic protons were located at 5.96 (dd, J = 2.04, 10.39 Hz) and 6.85 ppm (dd, J = 1.89, 10.39 Hz) . Rest of the spectral data was in conformity with the assigned structure (**2**).[14]



Scheme 3: a) H_2O_2, K_2CO_3, H_2O, THF, 0 °C , 6 h, 65 %; b) $NaBH_4$, MeOH, -40 °C, 15 min, 93 %; c) Im-C(=S)Im, C_6H_6, 80 °C , 12 h, 98 %; d) Bu_3SnH, AIBN, C_6H_6, 80 °C, 4 h, 30 %; e) MnO_2, CH_2Cl_2, 45 °C, 87%.

In conclusion we have reported for the first time the stereocontrolled synthesis of a novel and highly substituted cyclohexenone ring system of scyphostatin.

ACKNOWLEDGEMENT

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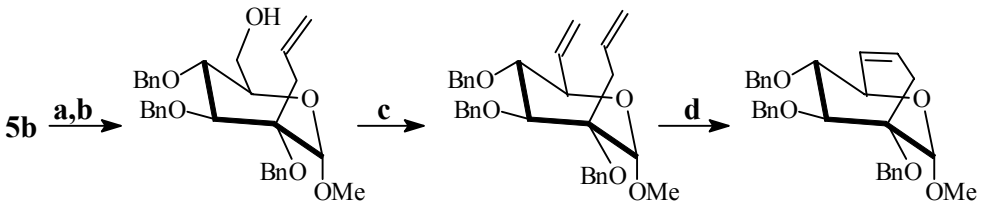

a) NaH, BnBr, DMF, rt, 90%; b) $LiAlH_4$, $AlCl_3$, Et_2O, CH_2Cl_2, 15 min, 95%; c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78^oC, 80%; (ii) $Ph_3P{=}CH_2$, THF, 65%; d) Grubbs catalyst, C_6H_5Me, reflux, 3 days, 45%.

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14. Structures of new compounds were established by ^{1}H NMR, FABMS/HRMS or microanalysis. The ^{1}H NMR spectral data of some key intermediates are given below:

5a (400 MHz, $CDCl_3$): 2.29 (dd, 1 H, J = 7.6, 15.3 Hz), 2.57 (dd, 1 H, J = 3.8, 15.3 Hz), 3.35 (s, 3 H), 3.65 (d, 1 H, J = 7.7 Hz), 3.83 (m, 2 H), 4.10 (m, 1 H), 4.32 (m, 1 H), 4.40 (s, 1 H), 4.65, 4.95 (ABq, 2 H, J = 15.6 Hz), 5.10 (m, 2 H), 5.60 (s, 1 H), 5.85 (m, 1 H), 7.30 (m, 10 H); **8** (200 MHz, $CDCl_3$): 2.27 (dd, 1 H, J = 9.0, 14.5 Hz), 3.09 (dd, 1 H, J = 4.5, 14.5 Hz), 3.27 (dd, 1 H, J = 6.8, 10.0 Hz), 3.38 (s, 3 H), 3.45 (m, 2 H), 3.75 (d, 2 H, J = 4.5 Hz), 4.52, 4.73 (ABq, 2 H, J = 10.2 Hz), 4.61, 4.79 (ABq, 2 H, J = 11.4 Hz), 4.65, 4.88 (ABq, 2 H, J = 10.9 Hz), 4.72 (s, 1 H), 5.11 (m, 2 H), 5.81 (m, 1 H), 7.30 (m, 15 H); **9** (200 MHz, $CDCl_3$): 1.29, 1.36 (2s, 6 H), 1.70 (dd, 1 H, J = 9.0, 15.9 Hz), 2.77 (dd, 1 H, J = 4.3, 15.9 Hz), 3.29 (dd, 1 H, J = 8.1, 11.3 Hz), 3.40 (s, 3 H), 3.47 (t, 3 H, J = 9.0 Hz), 3.75 (m, 2 H), 3.95 (dd, 1 H, J = 6.8 Hz), 4.20 (m, 1 H), 4.45 (s, 1 H), 4.63, 4.79 (ABq, 2 H, J = 11.5 Hz), 4.70, 4.90 (ABq, 2 H, J = 11.2 Hz), 4.75, 5.06 (ABq, 2 H, J = 11.5Hz), 7.30 (m, 15 H); **12** (200 MHz, $CDCl_3$): 1.15, 1.31 (2s, 6 H), 2.04 (m, 1H), 2.18 (dd, 1 H, J = 2.3, 15.9 Hz), 3.25 (m, 1 H), 3.56 (m, 2 H), 3.88 (d, 1 H, J = 9.0 Hz), 4.54, 4.77 (ABq, 2 H, J = 10.5 Hz), 4.61, 5.00 (ABq, 2 H, J = 11.4 Hz), 4.67, 5.11 (ABq, 2 H, J = 11.4 Hz), 4.68 (d, 1 H, J = 9.0 Hz), 6.04 (d, 1 H, J = 9.0 Hz), 6.90 (d, 1 H, J = 9.0 Hz), 7.30 (m, 15 H); **2** (500 MHz, $CDCl_3$): 1.22, 1.30 (2s, 6 H), 2.05 (dd, 1 H, J = 5.0, 13.8 Hz), 2.69 (dd, 1 H, J = 7.5, 13.7 Hz), 3.53 (t, 1 H, J = 7.7 Hz), 3.98 (d, 1 H, J = 7.4 Hz), 4.00 (t, 1 H, J = 7.6 Hz), 4.14 (m, 1 H), 4.42, 4.60 (ABq, 2 H, J = 11.6 Hz), 4.78 (s, 2 H), 4.75, 5.13 (ABq, 2 H, J = 11.6 Hz), 4.77 (ddd, 1 H, J = 1.9, 2.1, 7.7 Hz), 5.96 (dd, 1 H, J = 2.1, 10.4 Hz), 6.85 (dd, 1H, J = 1.89, 10.4 Hz), 7.3 (m, 15 H).