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An improved synthesis of the scyphostatin side-chain

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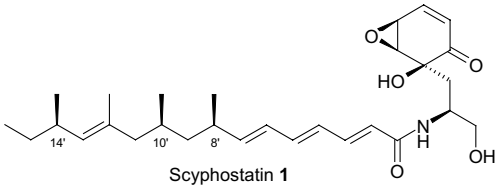
Abstract—A formal synthesis of the lipophilic side-chain of scyphostatin has been achieved using a convergent synthesis, in 16% yield over six steps. This synthesis involves enzymatic desymmetrisation of a *meso*-diol, resolution of 2-methylbutan-1-ol, stereoselective hydrozirconation of a volatile acetylene and a Negishi-style cross coupling.

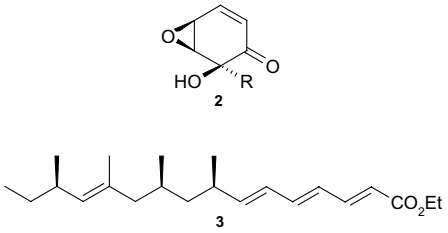
Scyphostatin **1** was first isolated in 1997 by Ogita et al. from the mycelial extract of the microorganism *Dasyscyphus mollissimus* SANK-13892,[1] and its structure assigned by spectroscopic and derivatisation methods. Degradation studies by Kogen et al.[2] established the absolute stereochemistry, and determined the 14′*R*, 10′*S*, 8′*R* configuration of the side-chain. It is one of a few natural products that selectively inhibit the enzyme neutral sphingomyelinase (N-SMase).[3] This makes it a lead candidate for the treatment of inflammatory and autoimmune disorders where ceramide, produced in the N-SMase mediated hydrolysis of sphingomyelin, plays a key role.



Scyphostatin **1**

In recent years, scyphostatin has become a popular synthetic target,[4] with most efforts concentrating on the highly functionalised cyclohexenone core, although no total synthesis has yet been reported. Indeed, we recently reported syntheses of analogues of the core **2** in both racemic[4a] and enantiopure forms.[4b] In 2000, Hoye and Tennakoon reported a stereoselective synthesis of the side-chain **3**,[5] the key steps of their synthesis involving formation of a terminal acetylene **5** from monoacetate **4** and the $AlMe_3$-mediated coupling of **5** with a lactate-derived triflate (Scheme 1). Oxidation of alcohol **7** followed by an immediate Horner–Wadsworth–Emmons olefination furnished ester **2** in 11 steps and 14% overall yield.

As part of our synthetic assault on scyphostatin, we required an efficient route to **3**. Our strategy for the formal synthesis of the side-chain is shown in Scheme 2. We envisioned alcohol **7** being formed through a Negishi-style cross coupling of vinyl iodide **8** with an organozinc reagent derived from iodide **9**. This could be synthesised from acetate **4** in a manner similar to Hoye,[5] whilst vinyl iodide **8** could be formed from acetylene **10** via a stereoselective hydrozirconation/iodination.



Our synthesis (Scheme 3) started with *meso*-diol **11**, easily available by reduction of dimethylglutaric anhydride.[6] Using the procedure developed by Achiwa et al.,[7a] treatment of **11** with vinyl acetate in the presence of porcine pancreatic lipase (PPL)[7] gave monoacetate **4** in 47% yield and in >95% ee.[8] Silylation with

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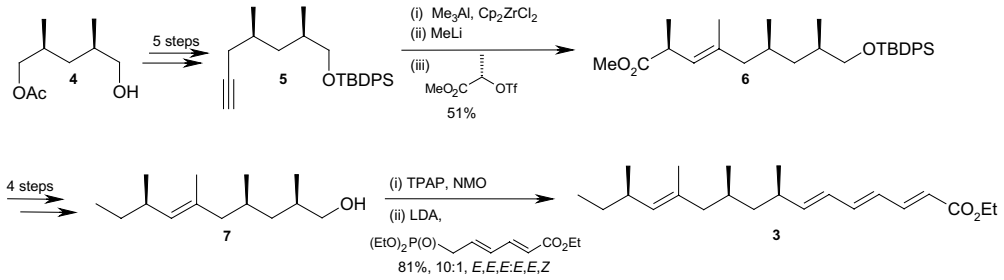
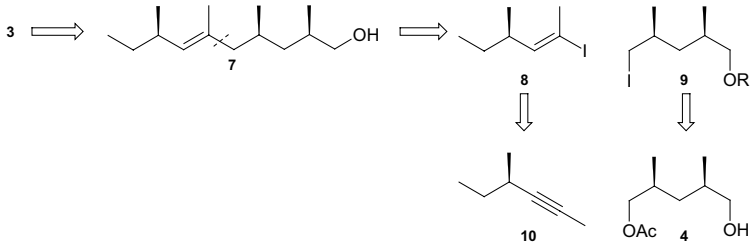
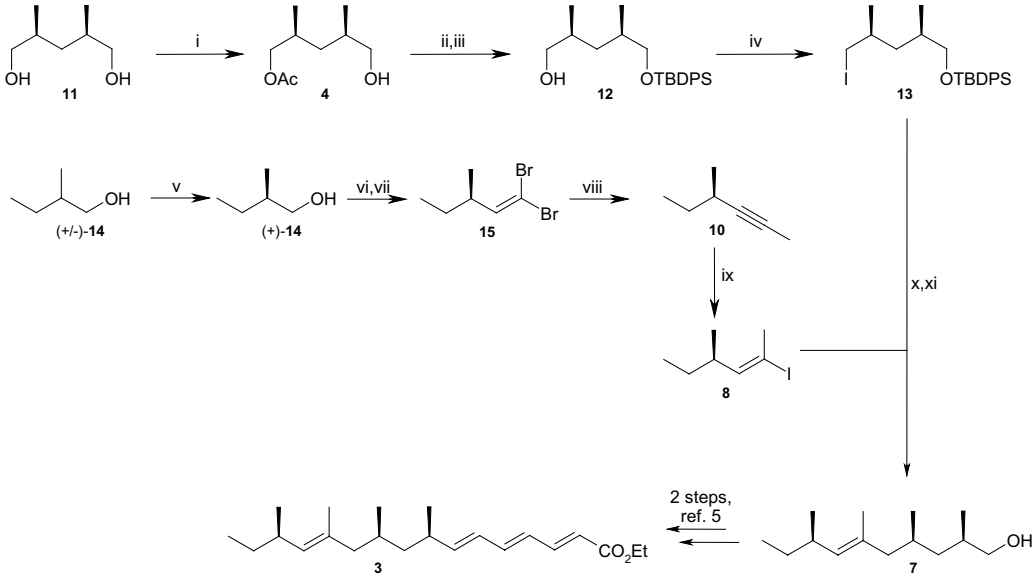


Scheme 1. Hoye's approach to the scyphostatin side-chain.[5]



Scheme 2. Retrosynthetic strategy.



Scheme 3. *Reagents and conditions*: (i) PPL, vinyl acetate, THF-H_2O, 47%; (ii) TBDPSCl, Et_3N, DMAP, CH_2Cl_2; (iii) K_2CO_3, MeOH, 89% (two steps); (iv) I_2, PPh_3, imidazole, CH_2Cl_2, 86%; (v) PFL, vinyl acetate, CH_2Cl_2, 30%; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −65 °C; (vii) PPh_3, CBr_4, CH_2Cl_2, 72% (two steps); (viii) *n*-BuLi, THF, −78 °C, then MeI, 84%; (ix) (a) Cp_2ZrCl_2, Super-Hydride, THF, then **10** (b) I_2/CCl_4, 73%; (x) $ZnCl_2$, *t*-BuLi, THF, 0 °C, then **8**, $Pd(PPh_3)_4$ (5 mol%), 66%; (xi) TBAF, THF, 68%.

tert-butyldiphenylsilyl chloride followed by acetate hydrolysis gave alcohol **12** (itself an intermediate in Hoye's side-chain synthesis)[5] in 89% yield over two steps. Finally, iodination with iodine and triphenylphosphine gave iodide **13** in 86% yield.[9]

For the vinyl iodide coupling partner **8**, we required (+)(*R*)-2-methylbutan-1-ol **14**. This was accessible through resolution of the racemate with *Pseudomonas fluorescens* lipase (PFL), in a procedure adapted from that of Effenberger.[10] Using this method, we obtained alcohol (+)-**14** in 30% yield and 90% ee.[8] Swern oxidation of the enantiomerically enriched alcohol, followed by Corey–Fuchs olefination[11] gave vinyl dibromide **15** in good overall yield. Treatment of **15** with *n*-butyllithium and iodomethane gave the volatile acetylene **10**.[12] This acetylene was treated with Schwartz's reagent (generated in situ from zirconocene dichloride and Super-Hydride®),[13] and the reaction quenched with a saturated solution of I_2 in CCl_4 to give vinyl iodide **8** as the sole

stereo- and regioisomer.[14] As mentioned above, we had planned to join our two coupling partners via a Negishi-type reaction.[15] To this end, we generated the corresponding organozinc reagent from iodide **13** using *tert*-butyllithium in the presence of anhydrous zinc chloride. Addition of vinyl iodide **8** and $Pd(PPh_3)_4$ gave a good yield of coupled product after chromatography,[16] with no traces of homocoupling. Desilylation with TBAF in THF gave the known alcohol **7** {$[\alpha]_D^{20} - 13.7$ (*c* 0.5, $CHCl_3$), lit.[5]; $[\alpha]_D^{25} - 14.4$ (*c* 1.10, $CHCl_3$)}.[16] Alcohol **7** has previously been converted into ester **3** in two steps (81%).[5]

In conclusion, we have completed a formal synthesis of the scyphostatin side-chain with a longest linear sequence of six steps, and with an overall yield of 16% from diol **11**. Our convergent approach, combined with the use of an enzymatic resolution of alcohol **14** makes the synthesis shorter and more efficient than that previously reported. Comparison of our observed optical rotation with the literature data[5] confirmed that stereochemical integrity was maintained throughout the synthesis. Application of this route to the synthesis of scyphostatin and its analogues is ongoing.

Acknowledgements

G.D.M. thanks the University of York for postdoctoral support.

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16. Synthesis of (2R, 4R, 6E, 8R)-tetramethyl-6-decen-1-ol 7: (a) Alkyl iodide **13** (606 mg, 1.26 mmol) and $ZnCl_2$ (0.5 M in THF, 2.5 mL, 1.25 mmol) were dissolved in anhydrous THF (10 mL) and cooled to −78 °C under argon. A solution of *tert*-BuLi (1.5 M in hexanes, 2.1 mL, 3.15 mmol) was added dropwise and then the pale yellow solution stirred at −78 °C for 10 min, then for 20 min at rt. This solution was transferred by cannula to a stirred suspension of vinyl iodide **8** (236 mg, 1.06 mmol) and $Pd(PPh_3)_4$ (61 mg, 0.05 mmol, 5 mol%) in THF (6 mL) under argon and the resulting brown suspension stirred at rt in the dark overnight. The reaction was quenched with saturated $NaHCO_3$ (20 mL), then extracted into Et_2O (2×50 mL). The combined organic extracts were washed with saturated brine solution (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica (2% Et_2O in PE) gave the coupled product (312 mg, 0.69 mmol, 66%) as a pale yellow oil; $[\alpha]_D^{20} + 3.0$ (*c* 1.0, $CHCl_3$); found (CI): MH^+, 451.34047. $C_{30}H_{46}OSi$ requires MH^+, 451.33962, 1.9 ppm error; $R_f = 0.53$ (2% Et_2O in PE); υ_{max}/cm^{-1} (thin film) 2957, 2929, 2858, 1471, 1428, 1388, 1363, 1158, 1111; δ_H (400 MHz, $CDCl_3$) 7.70–7.67 (4H, m, Ph–H), 7.44–7.37 (6H, m, Ph–H), 4.85 (1H, d, *J* 9.4, 7-H), 3.53 (1H, dd, *J* 5.5, 10.8, 1-H_A), 3.43 (1H, dd, *J* 4.3, 10.8, 1-H_B), 2.29–2.20 (1H, m, 8-H), 2.04–1.96 (1H, m, 5-H), 1.82–1.73 (1H, m, 2-H), 1.64–1.60 (2H, m, 4, 5-H), 1.54 (3H, d, *J* 1.2, 6-CH_3), 1.37–1.28 (4H, m, 3-H_2, 9-H_2), 1.07 (9H, s, *t*-Bu), 0.96 (3H, d, *J* 6.4, 8-CH_3), 0.92 (3H, d, *J* 6.7, 2-CH_3), 0.87–0.82 (6H, m, 4-CH_3, 10-CH_3); δ_C (100 MHz, $CDCl_3$) 135.6 (CH), 134.1 (C), 132.9 (CH), 132.4 (C), 129.5 (CH), 127.5 (CH), 68.9 (CH_2), 47.9 (CH_2), 41.2 (CH_2), 34.1 (CH_2), 33.2 (CH), 30.5 (CH), 28.2 (CH), 26.9 (CH_3), 21.1 (CH_3), 19.9 (CH_3), 18.1 (C), 17.8 (CH_3), 16.1 (CH_3), 12.0 (CH_3); *m/z* (CI) 451, 355 (100%), 314, 196; (b) 273 mg (0.61 mmol) of the silyl ether was dissolved in anhydrous THF (5 mL) under argon. A solution of TBAF (1 M in THF, 0.73 mL, 0.73 mmol) was added and the reaction stirred at rt for 6 h. The reaction was quenched with brine (10 mL) and extracted into Et_2O (2×10 mL), the combined organic extracts washed with

brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica (6:1 PE–EtOAc) gave alcohol **7** (87 mg, 0.41 mmol, 68%) as a colourless oil, $R_f = 0.24$ (6:1, PE–EtOAc); $[\alpha]_D^{20}$ –13.7 (*c* 0.5, $CHCl_3$), lit.[5] $[\alpha]_D^{25}$ –14.4 (*c* 1.10, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.85 (1H, d, *J* 9.2, 7-H), 3.53 (1H, dd, *J* 5.2, 10.7, 1-H_A), 3.37 (1H, dd, *J* 6.7, 10.7, 1-H_B), 2.27–2.20 (1H, m, 8-H), 2.03–1.98 (1H, m, 5-H), 1.77–1.63 (3H, m, 2, 4, 5-H), 1.56 (3H, d, *J* 1.6, 6-CH_3), 1.36–1.27 (3H, m, OH, 9-H_2), 1.26–1.17 (2H, m, 3-H_2), 0.94 (3H, d, *J* 6.7, 8-CH_3), 0.91 (3H, d, *J* 6.4, 2-CH_3), 0.84 (3H, t, *J* 7.3, 10-CH_3), 0.82 (3H, d, *J* 6.1, 4-CH_3).