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Highly diastereoselective total synthesis of the anti-tumoral agent (±)-Spisulosine (ES285) from a Morita–Baylis–Hillman adduct

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ABSTRACT

We disclose herein a new approach for the highly diastereoselective total synthesis of the anti-tumoral agent (±)-Spisulosine. The synthesis was accomplished in seven steps with an overall yield of 10%. The key step involves the transformation of a Morita–Baylis–Hillman into an acyloin, which was subsequently used as substrate in a highly diastereoselective reductive amination reaction.

The Ocean is not only an important food source for human beings but its marine life is also a rich source of new chemicals. The systematic search from marine biota constitutes an important strategy for the discovery of new lead compounds.[1] The marine natural products have been shown to display huge structural diversity normally associated with important biological activity (Fig. 1).

The first drug from the sea, Ziconotide (ω-conotoxin MVIIA, **1**) is a peptide that was originally isolated from a tropical marine cone snail.[2] Trabectedin (**2**, Fig. 1) (Yondelis®/ecteinascidin-743/ET-743) is an anti-tumoral alkaloid derivative found in a tropical sea-squirt (*Ecteinascidia turbinate*) that resides in the Caribbean sea.[3,4] Hemiasterlin A and B (**3** and **4**) were isolated some years ago from sponges of the genus *Auletta* and *Cymbastella* and displayed a highly potent cytotoxic activity.[5]

Searching for new cytotoxic compounds from a natural origin, Reinhart et al.[6] carried out a biologically guided screening of extracts obtained from the clam *Spisula polynyma*. The extracts (toluene, DCM, AcOEt and *n*-butanol) were essayed against L1210 cells for significant cytotoxicity. Cytotoxicity was observed in the initial crude, DCM and toluene extracts, and from these extracts, Spisulosine (**5**, Fig. 2) was isolated as the most bioactive compound.

Spisulosine (**5**) is a sphingoid-type base which presents a long unsaturated alkyl chain (C_{18}) and a 1,2-aminoalcohol motif in a *anti* relationship.

Cultured cells showed altered morphology on treatment with Spisulosine (**5**). Studies confirmed that Spisulosine (ES285) works on the cell's microfilaments but not on the microtubule network.[7] Spisulosine inhibits the growth of the prostate tumor cell lines PC-3 and LNCaP and could have a role as prostate anti-tumoral agent.[8]

The structural simplicity associated with the antiproliferative activity of **5** has stimulated several elegant and efficient approaches for its total synthesis.[6,9]

The quite impressive biological activity of Spisulosine calls for the preparation of alternative analogues given its important antitumoral activity. Morita–Baylis–Hillman[10] is a remarkable chemical transformation permitting access to highly functionalized products,[11] that can also be valuable starting materials in natural product synthesis.[12]

Recently, we have developed a new and straightforward approach for the preparation of acyloins from Morita–Baylis–Hillman adducts.[13] This method is based on using a very facile Curtius rearrangement methodology to form the acyloin from the carboxylic acid. A suitable acyloin (**6**) can then be the substrate for a diastereoselective reductive amination, and afford Spisulosine (**5**) (Scheme 1).

The synthesis begins with the oxidation of commercial hexadecanol (**8**) with PCC in refluxing dichloromethane to provide the hexadecanal (**9**) in 95% yield after 2 h. Morita–Baylis–Hillman reaction between **9** and methyl acrylate and DABCO at 50 °C furnished **7** in 60% (Scheme 2).[14] In an attempt to improve the yield we tested several experimental modification (use of octanol,[15] utrasound,[16] and water/ionic liquid/microwave[17]). In all cases, the reaction afforded the desired product, but in lower yields. Apparently, long-chain aldehydes are troublesome substrates for the Morita–Baylis–Hillman reaction and perhaps this restriction explains the few reports on the use of such substrates using this protocol.[18]

Adduct **7** was then silylated in the presence of TBSOTf/Et_3N to afford the corresponding silyl ether **10**, in 70% yield. After filtration through a silica gel column, ester hydrolysis gave the silyl ether-acid **11** in nearly quantitative yield. The acid **11** was then obtained in three steps with an overall yield of 42% from hexadecanal (Scheme 2). Acid **11** was then used as substrate for a Curtius rearrangement.[19] The synthesis of **6** from **11** was operationally very simple and was performed as a one-pot reaction. The only operation performed amongst these synthetic steps was the removal of reaction solvent.

Acid **11** was treated with ethyl chloroformate, for 5 min at 5 °C, to afford the corresponding carbonate, followed by the addition of

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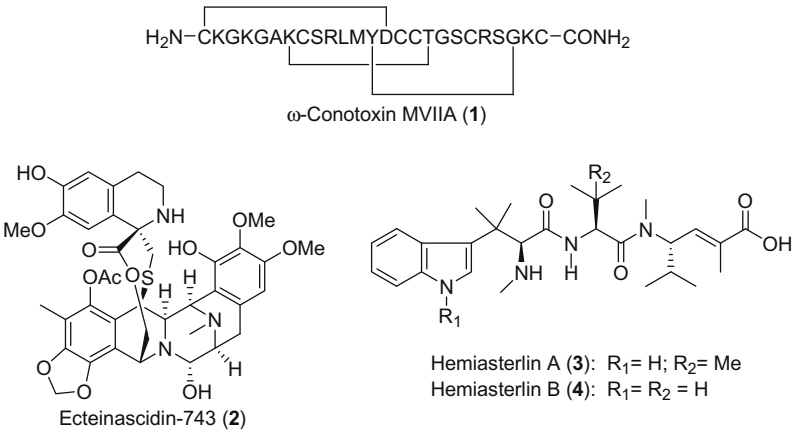


Figure 1. Examples of the structural diversity found in marine natural products.

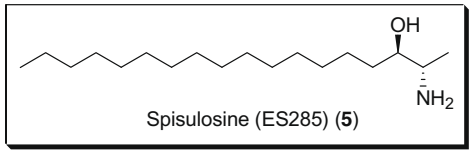
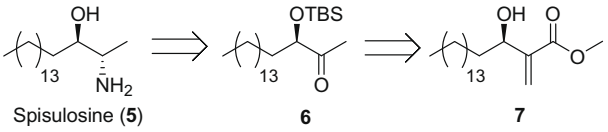
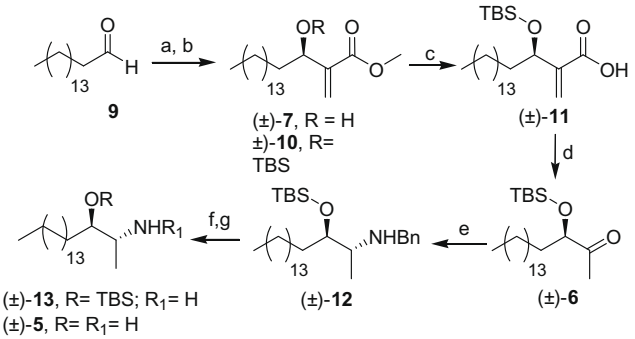


Figure 2. Spisulosine structure.



Scheme 1. Retrosynthetic analysis of Spisulosine (**5**).



Scheme 2. Reagents and conditions: (a) methyl acrylate, MeOH, DABCO, 50 °C, 96 h, 60%; (b) TBSOTf, Et_3N, CH_2Cl_2, t.a, 6 h, 70%; (c) NaOH, MeOH/H_2O (1:1), 70 °C, 30 h, quantitative; (d) (i) $ClCO_2Et$, acetone, 5 °C, 5 min; (ii) NaN_3, rt, 2 h; (iii) toluene, reflux, 2 h; (iv) H_2O, reflux, 12 h, 40% overall yield; (e) NH_2Bn, CH_2Cl_2, 40 °C to rt, then $NaBH_3CN$, 20 h, rt, 70%; (f) Pd/C, H_2, AcOH, CH_2Cl_2, 50 °C, 20 h, 90%; (g) HCl, MeOH/CH_2Cl_2, 50 °C, 20 h, 98%.

solid sodium azide under vigorous stirring. After solvent removal, the acyl azide formed was diluted in toluene and rearranged under thermal conditions after 2 h to give an ene-isocyanate intermediate. After the removal of toluene, the aforementioned intermediate was refluxed in water to provide acyloin **6** in 40% overall yield.

Searching for ways to shorten this synthetic sequence, we tested DPPA (diphenylphosphoryl azide) as an alternative reagent for the Curtius rearrangement.[20] Unfortunately, in our hands this reaction failed to give the desired product and the formation of several byproducts was detected by TLC.

To finish the sequence, acyloin **6** was initially treated with benzylamine to form an imine, which was immediately reduced with sodium cyanoborohydride to give the aminoalcohol **12** in 70% yield. The diastereoselectivity of this step is very high as confirmed by ^1H NMR analysis.[21] Debenzylation was performed in the presence of hydrogen catalyzed by 5% Pd on carbon to give the amine **13** in 90% yield. Finally, the amine was treated with HCl in a DCM/MeOH mixture to remove the silyl group to afford Spisulosine in 98% yield. We have tried with no success to remove the protecting groups in a single step.

All spectroscopic and physical data are identical to those described in the literature for natural and synthetic Spisulosines.[6a,9,22]

In summary, Spisulosine was synthesized in seven steps from hexadecanal with an overall yield of 10%. The strategy is very simple and requires no special conditions such as low temperature or dry solvents. The reagents used are routinely found in organic synthesis laboratories. If the sequence begins with adduct **7** in its enantiomerically pure form, it would allow the asymmetric synthesis of Spisulosine. Other Spisulosine derivatives can also be synthesized using the sequence described herein.[6a]

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3. Yondelis is a registered trademark of Zeltia (Pharma Mar), licensed to Jonhson and Johnson in USA.
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22. Spectral data for (±)-Spisulosine: IR (Film, ν_{max}): 3348, 3297, 2955, 2919, 2851, 1607, 1471 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$), δ ppm: 3.39–3.47 (m, 1H), 2.88–3.06 (m, 1H), 1.64–1.88 (sl, 3H), 1.20–1.40 (m, 28H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$), δ ppm: 74.7, 50.3, 32.4, 31.9, 29.8, 29.7, 29.6, 29.3, 26.2, 22.7, 16.8, 14.1. HRMS (ESI) Calcd for $C_{18}H_{34}ON$ $[M+H]^+$ 286.3110; Found 286.3088.