An efficient total synthesis of the anticancer agent (+)-spisulosine (ES-285) from Garner's aldehyde

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ABSTRACT

An efficient total synthesis of (+)-spisulosine (ES-285) was completed in nine steps from (*S*)-Garner's aldehyde. The vicinal amino alcohol moiety with anti-configuration was achieved by a highly diastereo-selective addition of vinyl magnesium bromide to Garner's aldehyde. The long hydrocarbon chain of the antitumor natural product was installed via olefin cross metathesis of the benzyl-protected allylic alcohol with an appropriate olefin counterpart followed by hydrogenation.

Natural products have played a prominent role in the history of drug discovery and development process by providing novel, clinically useful medicines having various biological activities such as anticancer, antiprotozoal, antifeedant, anathematic, antiepileptic, and antimicrobial activities, amongst others.[1] In the last decades, natural products, specially having anticancer activity received increased attention from chemists because cancer is now the most frequent disease and has got the first place in the order of causes of deaths[2] in the developed countries. So there is always an ever increasing requirement of safe and effective antitumoral agents to control cancer.

The influence of natural products upon anticancer drug discovery and design is very impressive as about 75% of all drugs now in clinical trials for cancer treatment are either natural products or pharmacophores derived from natural products.[3] (2*S*,3*R*)-2-Amino-3-octadecanol (spisulosine or ES-285 **1**; Fig. 1) is a marine-derived bioactive compound isolated by Rinehart et al.[4] from the North Arctic clam *Spisula polynyma.* (+)-Spisulosine is a sphingoid-type base which contains a long saturated C_{18} alkyl chain with an *erythro*-1,2-amino alcohol. This naturally occurring substance was found to exhibit potent cytotoxicity and morphological alteration against L1210 leukemia cells. It also showed in vitro activity against P-388 (0.01 µg/ml); HT-29 (0.05 µg/ml) and MEL-28 (0.05 µg/ml) tumor cell lines.[4]

The great antiproliferative activity[5] of (+)-spisulosine toward advanced malignant solid tumors[6] included it in clinical trials as a potential antitumoral agent. Owing to its simple structure and potent biological activity it has garnered much attention from the synthetic community. Several approaches for its synthesis have been disclosed. The first total synthesis of (+)-spisulosine was reported from L-alanine methyl ester hydrochloride.[4] A formal synthesis of (+)-spisulosine was achieved by Lee and co-workers from chiral 2-aziridine carboxylate.[7] The asymmetric synthesis of (+)-spisulosine from the *N*-benzylimine derived from D-mannitol[8] was completed by Allepuz et al. Later, Séguin et al. reported on the total synthesis of the title natural product from enantiopure *N*-*tert*-butylsulfinyl imine.[9] Very recently in this year Coelho and co-workers reported a total synthesis of (±)-spisulosine starting from hexadecanal[10] involving Morita–Baylis–Hillman (MBH) chemistry. Our ongoing interest toward the total synthesis of bioactive natural products and their analogues stimulated us to explore a convenient approach to the asymmetric synthesis of this interesting natural product.[11]

Herein, we would like to report a new approach to the total synthesis of (+)-spisulosine starting from easily available (*S*)-Garner's aldehyde. In our approach, the hydroxy group at C_3 of the natural product was introduced by highly diastereoselective nucleophilic addition on Garner's aldehyde resulting in a terminal allylic alcohol. Later, this intermediate was used in olefin cross metathesis with 1-pentadecene to complete the synthesis of the title anticancer agent.

The retrosynthetic strategy for (+)-spisulosine (**1**) is delineated in Scheme 1. We envisaged that **1** could be obtained from protected amine **C**, a synthetic precursor of (+)-spisulosine, by hydrogenation of the double bond and cleavage of protecting groups. The intermediate **C** could in turn be prepared by subjecting the functionalized olefin **B** to coupling with a required long chain olefin counterpart involving cross metathesis strategy. The fragment **B** could be prepared from intermediate **A** involving a sequence of reactions. Intermediate **A**, which contains the required *erythro*-1,2 amino alcohol of the natural product, could be obtained by highly
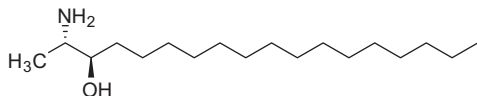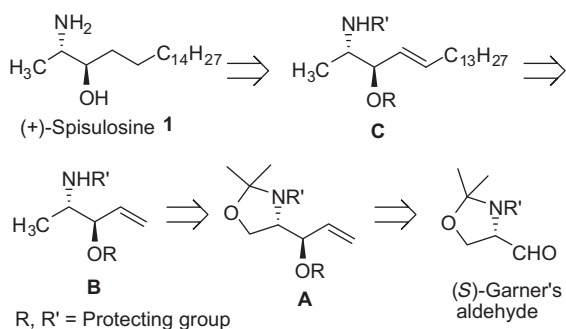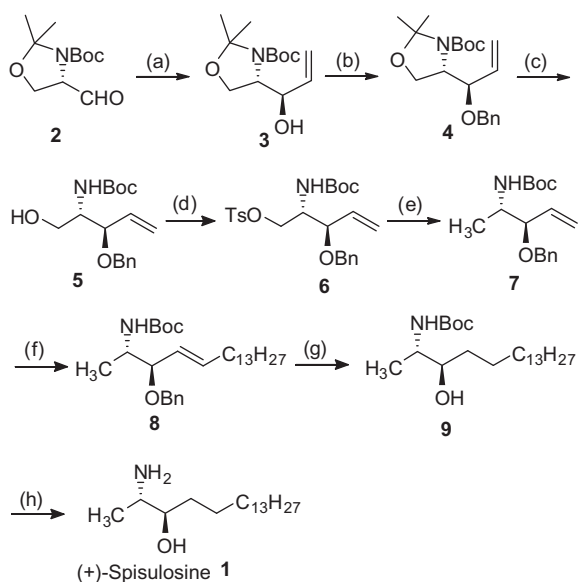
Figure 1. Structure of (+)-spisulosine or ES-285 (**1**).

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Scheme 1. Retrosynthetic analysis of (+)-spisulosine **1**.

Scheme 2. Synthesis of (+)-spisulosine (**1**). Reagents and conditions: (a) Vinyl magnesium bromide, THF, −78 °C, 74%; (b) Benzyl bromide, NaH, DMF, 91%; (c) PTSA, MeOH, 0 °C, 84%; (d) TsCl, Et₃N, DCM, 25 °C, 73%; (e) LiAlH₄, THF, −20 °C, 80%; (f) Grubbs' second generation catalyst (5 mol%), 1-pentadecene, DCM, reflux, 87%; (g) H₂, Pd/C, MeOH—CHCl₃, 91%; (h) (i) HCl-dioxane, rt; (ii) Aq. NaOH, DCM, rt, 90%.

Table 1

Optimization of cross metathesis reaction of **7** in DCM with 1-pentadecene in the presence of 5 mol % Grubbs' second generation catalyst

Entry	Equivalent of 1-pentadecene	Yield of **8** (%)
1	1	70
2	2	79
3	**3**	**87**
4	5	89

diastereoselective Grignard addition to (S)-Garner's aldehyde at low temperature.

Thus, as per retrosynthesis shown above, the convergent total synthesis of (+)-spisulosine (**1**) was commenced from (S)-Garner's aldehyde which could be easily prepared from commercially available inexpensive ʟ-serine.[12] Stereoselective addition of vinyl magnesium bromide to freshly prepared Garner's aldehyde **2** at −78 °C afforded a mixture of *anti* and *syn* allylic alcohols in 6:1 ratio[13a,13b] from which the major *anti* isomer **3** was separated by column chromatography. It has already been reported that vinyl magnesium bromide is a better Grignard species[13] compared to other Grignard reagents for asymmetric Grignard addition to Garner's aldehyde. The alcohol functionality of compound **3** was protected as O-benzyl ether to furnish **4** followed by smooth isopropylidene opening with PTSA in MeOH at 0 °C to obtain intermediate **5**. Now to complete the synthesis of compound **7**, the free hydroxymethyl group at C₁ in compound **5** had to be converted into methyl group and this could be done in two steps, first by tosylation[13b] of the primary alcohol followed by its replacement by hydride. Thus, the tosylation of alcohol **5** with tosyl chloride in the presence of triethylamine and subsequent treatment of the tosyloxy derivative **6**[14] with LiAlH₄ afforded the desired olefin **7** in 80% yield (Scheme 2).

With the assembly **7** with us, our next attempt was focused toward the installation of appropriate long alkyl chain of the natural product and this was done by adopting cross metathesis approach. The cross metathesis[11a] reaction between olefin **7** and 1-pentadecene in the presence of Grubbs' second generation catalyst (5 mol %) gave the compound **8**. It was observed that by increasing the equivalents of 1-pentadecene the yield of cross metathesis product was enhanced and therefore, when 3 equiv of alkene was used in this reaction the cross metathesis product **8** was obtained in 87% yield (Table 1).

In the next step, the hydrogenation of double bond and removal of benzyl ether protection of compound **8** were carried out smoothly in the presence of H₂ atmosphere and 10% Pd/C in MeOH/CHCl₃ (2:1) to afford compound **9** as a white solid in 91% yield.[15]

Now acidic hydrolysis of **9** in a solution of dioxane saturated with HCl gas furnished the corresponding HCl salt of (+)-spisulosine (ES-285·HCl). The targeted natural product (+)-spisulosine **1** (ES-285) was finally obtained in 90% yield after neutralization of the hydrochloride salt by aqueous NaOH solution (Scheme 2). All the spectroscopic and physical data[16] are identical to those reported in the literature.[4a,7,8]

In summary, we have achieved a convergent total synthesis of (+)-spisulosine or ES-285 (**1**) by utilizing an olefin cross metathesis reaction between long chain olefin 1-pentadecene and compound **7** with a terminal double bond followed by catalytic hydrogenation of the resulting compound. The enantiomer of this natural product could also be synthesized by using this approach. Since the title natural product **1** was found to exhibit great antiproliferative activity toward advanced malignant solid tumors and is now in clinical trials, this class of compounds and their analogues thus may deserve interest as potent and safe anticancer agents. Therefore, one can install different cross olefin counterparts[9] by adopting this flexible approach to facilitate the synthesis of various analogues of the title natural product for improved antitumor activity.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.146.

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14. The tosylate **6** was not stable and it was used immediately for the next step, that is, for its LiAlH$_4$ reduction.

15. The physical and spectroscopic data of compound **9** are identical to those reported in the literature except the specific rotation. The specific rotation of the compound **9** $\{[\alpha]_D^{28} = -8.54$ (c 0.71, CHCl$_3$)$\}$ does not match with that reported by Lee and co-workers $\{$Ref. 7 $[\alpha]_D^{24} = +15.2$ (c 1.00, CHCl$_3$)$\}$ but closer to the value reported by Allepuz et al. $\{$Ref. 8 $[\alpha]_D^{25} = -4.4$ (c 1.00, CHCl$_3$)$\}$.

16. Physical and spectroctroscopic data of ES-285 or (+)-spisulosine **1**: Yield: 90%; white solid compound; Mp 65–67 °C $\{$Ref. 8 Mp 64.5–66 °C$\}$; $[\alpha]_D^{28} = +25.3$ (c 0.95, CHCl$_3$)$\{$Ref. 4a $[\alpha]_D^{26} = +24.9$ (c 1.00, CHCl$_3$), Ref. 8 $[\alpha]_D^{25} = +24.0$ (c 1.00, CHCl$_3$)$\}$. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 0.84$–0.88 (m, 3H), 0.99 (d, $J = 6.4$ Hz, 3H), 1.24–1.37 (br m, 27H), 1.46–1.48 (br m, 1H), 1.83 (br s, 3H), 2.94 (br m, 1H), 3.42 (br m, 1H). ^{13}C (75 MHz, CDCl$_3$): $\delta = 14.5$ (CH$_3$), 17.3 (CH$_3$), 23.1 (CH$_2$), 26.6 (CH$_2$), 29.7–30.2 (10 × CH$_2$), 32.3 (CH$_2$), 32.9 (CH$_2$), 50.8 (CH), 75.1 (CH). IR (neat, cm^{-1}): 3752, 3448, 2920, 2361, 1628, 771. DART–HRMS: m/z [M+H]$^+$ calcd for C$_{18}$H$_{40}$N$_1$O$_1$ 286.3110, found 286.3119.