A Concise Synthetic Approach to (+)-Valienamine Starting from Garner's Aldehyde

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Abstract: A synthesis of (+)-valienamine was achieved starting from Garner's aldehyde in ten steps and 23% overall yield. A unique feature of the synthetic route is that an acyclic precursor was constructed, using diastereoselective antireductive coupling reaction of alkyne and Garner's aldehyde as the key step, which was then cyclized in an intramolecular aldol reaction to form the valienamine skeleton.

Key words: (+)-valienamine, Garner's aldehyde, diastereoselective, hydrozirconation–transmetalation, intramolecular aldol reaction

Valienamine (**1**) is an α-glucosidase inhibitor[2] that was isolated from the microbial degradation of validoxylamine A (**2**) with *Pseudomonas denitrificans*,[3] *Flavobacterium saccharophilum*,[4] or from the NBS cleavage of validoxylamine A or its derivatives (Figure 1).[5] Moreover, valienamine (**1**) is also an essential core unit in many kinds of pseudo-oligosaccharidic α-D-glucosidase inhibitors.[6] In view of these desirable properties, a considerable amount of effort[7–10] has been put into the enantiospecific syntheses of valienamine, among which most reported total syntheses employ cyclitol quebrachitol,[7] D-glucose derivatives,[8] or (–)-quinic acid[9] as the chiral building block. However, such strategies are often limited by the use of relatively expensive chiral building blocks and/or the need for lengthy protecting-group manipulation. In some other methods the cyclohexene skeleton of **1** was constructed through Diels–Alder reaction or ring-closing metathesis of an acyclic diene.[10] In this letter, we report a novel synthetic approach that leads from a construction of an acyclic precursor and its cyclization at a later stage to form the valienamine skeleton.

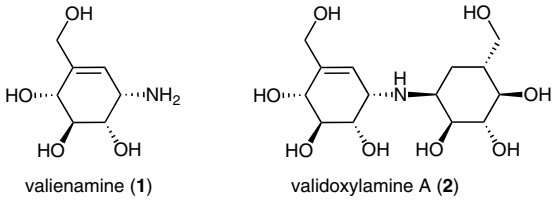
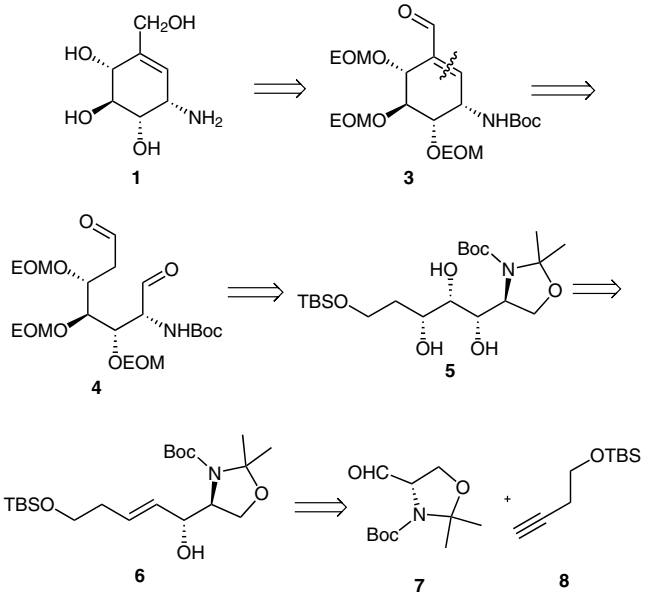


Figure 1

We reasoned that **1** can be obtained by Luche reduction of aldehyde group and removing ethoxymethyl and Boc protecting group in **3** (Scheme 1). Disconnection via intramolecular aldol condensation led to the acyclic precursor **4**. The requisite precursor **4** can in turn be synthesized from the monoprotected tetraol **5**, the product of a diastereoselective dihydroxylation of **6**. We envisioned that the highly functionalized key intermediate **6** could be obtained by reductive coupling of Garner's aldehyde **7**[11] and protected 3-butyn-1-ol **8**, which is commercially available. Compounds **7** and **8** can also be synthesized from readily available starting materials L-serine and 3-butyn-1-ol, respectively.



Scheme 1 Retrosynthetic analysis of **1**

Generally, the design of addition of nucleophiles to α-chrial aldehyde **7** could be based on models of either chelation-control transition state[12] or Felkin–Anh transition state,[13] which would lead to *syn* or *anti* addition. Some methodologies for alkyne addition of Garner's aldehyde have been previously investigated,[14] and Herold[14a] and coworkers further investigated the effect of additives and found that the *anti* selectivity increased in the presence of HMPA, a cation-complexing agent. However, this type of alkyne-addition method requires an additional step, that

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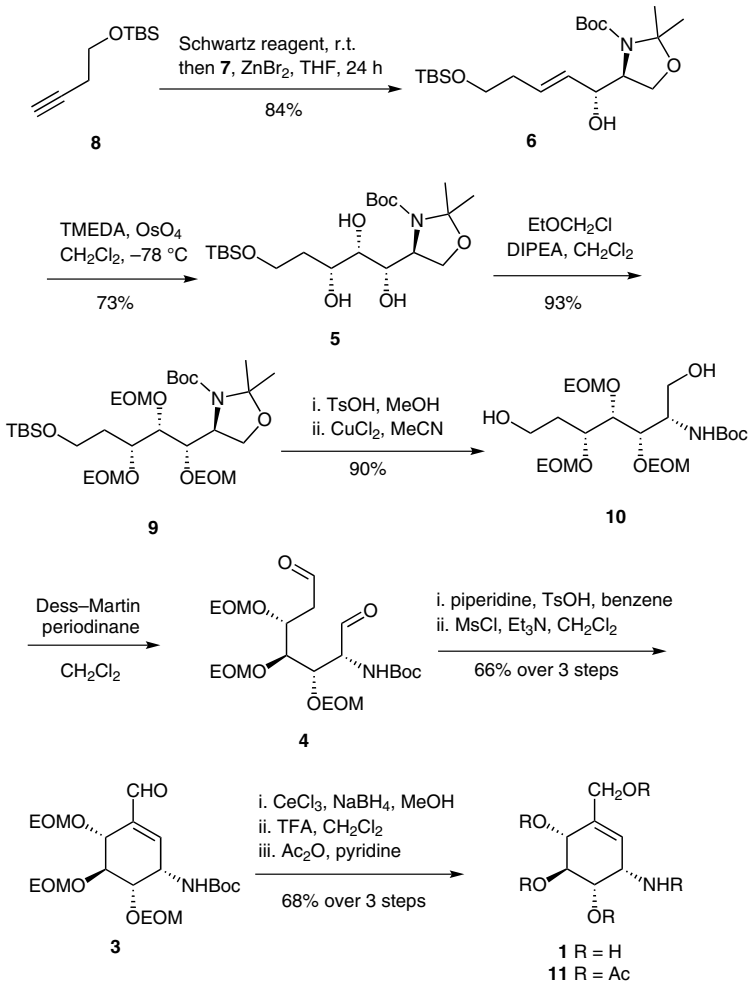
is, reduction of the triple bond to an *E*-olefin. In the search for a complementary method for producing the *anti* diastereomer we turned to vinylzinc nucleophiles, generated conveniently from an alkyne such as **8** by a hydrozirconation–transmetalation sequence,[15] which have been reported to add to Garner's aldehydes with high *anti* diastereoselectivity in the presence of $ZnBr_2$.[16] Herein we further show the utility of this reaction.

As depicted in Scheme 2, treatment of **8** with zirconocene hydrochloride[15] in THF, followed by addition of Garner's aldehyde **7** and $ZnBr_2$ delivered the desired allylic alcohol **6**[17] in good yield (84%) with virtually complete diastereocontrol (*anti*/*syn* > 15:1). The ratio of *anti*/*syn* was determined by HPLC analysis. Similar results regarding the diastereoselectivity have been published by Murakami et al.[16] Dihydroxylation of allylic alcohol using osmium tetroxide with TMEDA[18] produced the *syn*,*syn*-triol **5** in an acceptable 73% yield with a small amount of *syn*,*anti* diastereomer (15%). The diastereoselectivity was good (*syn*/*anti* = 4.5:1~5:1), and the unwanted *syn*,*anti* diastereomer could be separated by column chromatography at this point. When AD-mix-β was used, the product obtained was a 2:1 mixture of the diastereomeric triols, with the desired *syn*,*syn* diastereomer as the major product.

With all the stereocenters in place, we set out to prepare for the cyclization. Exposure of triol **5** to EOMCl gave compound **9** in 93% yield. The ^{13}C NMR spectra of compound **9** was complex due to the presence of the Boc protecting group, which resulted in a number of rotational isomers at 23 °C. Selective deprotection of TBS ethers by exposure of **9** to TsOH in MeOH, followed by removal of the *N*,*O*-acetonide with $CuCl_2$ in MeCN provided diol **10** in 90% yield for the two steps.

In order to execute the planned aldol-type cyclization, the terminal dihydroxy group needed to be oxidized to the level of aldehyde. A protocol involving Dess–Martin periodinane oxidation was found to be superior to other conditions, and the desired dialdehyde **4**, without further purification, was directly converted to the six-membered ring structure **3** through an intramolecular aldol condensation reaction under mild conditions[19] (cat. TsOH, piperidine, r.t., 2 h), followed by β-elimination of the formed hydroxyl group with MsCl and Et_3N. Attempt at other intramolecular aldol condensation cyclization conditions[20] failed to give our desired compound **3**. Thus, the intramolecular aldol-type cyclization provided the valienamine skeleton. Controlled reduction of enal **3** with $NaBH_4$ in methanol solution containing cerium chloride, followed



Scheme 2 Synthesis of valienamine (**1**) from Garner's aldehyde

by removal of the EOM ether and Boc in TFA–CH_2Cl_2 provided (+)-valienamine (**1**), which was characterized as its pentaacetate **11**[21] (68%). Comparison of the physical properties to those recorded confirms its identity.[9b] This synthesis, based on a diastereoselective *anti*-reductive coupling reaction of alkyne and chiral aldehyde followed by intramolecular aldol-type cyclization, requires ten steps from readily available Garner's aldehyde **7** to give (+)-valienamine in 23.0% overall yield.

In conclusion, a synthesis of (+)-valienamine was achieved starting from Garner's aldehyde and well-established, highly efficient reactions were employed in this synthesis. A unique feature of the synthetic route is that an acyclic precursor was constructed, which was then cyclized in an intramolecular aldol reaction to form the (+)-valienamine skeleton.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Procedure for the Synthesis of 6**
To an ice-cooled stirred suspension of $Cp_2Zr(H)Cl$ (5.05 g, 19.6 mmol) in THF (50 mL) under argon protection was added *tert*-butyl(but-3-ynyloxy)dimethylsilane (3.61 g, 19.6 mmol), the mixture was stirred at r.t. for 1 h, and then cooled to 0 °C. To the resulting orange solution was added aldehyde **7** (2.25g, 9.8 mmol) in THF (35 mL) followed by $ZnBr_2$ (552 mg, 2.45 mmol, dried under vacuum for 1 h before use), and the mixture was stirred for 24 h at r.t. The mixture was diluted with EtOAc (100 mL) and aq potassium sodium (+)-tartrate (5.7 g, 19.6 mmol), and stirred for 10 min. The resulting suspension was filtered off and washed thoroughly with EtOAc (100 mL). The combined filtrate was transferred into a separatory funnel and successively washed with H_2O and brine. The aqueous phase was extracted with EtOAc (2 × 200 mL), and the combined organic layers were dried over anhyd Na_2SO_4. The mixture was concentrated and purified by silica gel chromatography to afford **6** (3.625 g, 84%) as a colorless oil: $[\alpha]_D^{20}$ –27.0 (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.72 (m, 1 H), 5.49 (dd, *J* = 15.0, 6.0 Hz, 1 H), 4.02 (m, 4 H), 3.61 (t, *J* = 6.0, 2 H), 2.26 (m, 2 H), 1.48 (s, 15 H), 0.86 (s, 9 H), 0.01 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 130.6, 128.7, 94.1, 80.7, 73.6, 64.7, 62.7, 61.9, 35.9, 28.2, 28.2, 28.2, 26.3, 25.8, 25.8, 25.8, 24.5, 18.1, –5.4, –5.4. IR (film): 3454, 2931, 2858, 1699, 1473, 1387, 1255, 1174, 1097, 837, 775 cm^{-1}. MS (EI): *m/z* (%) = 415 (0.04)[M^+], 100 (64.29), 57 (100.00). HRMS (EI): *m/z* calcd for $C_{21}H_{41}NSiO_5$ [M^+]: 415.2754; found: 415.2765.
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(21) **Procedure for the Synthesis of 11**
To a suspension of **3** (40 mg, 0.09 mmol) and $CeCl_3 \cdot 7H_2O$ (52 mg, 0.135 mmol) in MeOH (3 mL) was added $NaBH_4$ (4 mg, 0.1 mmol) at 0 °C. The mixture was stirred for 15 min, and the solvent was removed under reduced pressure. Then, H_2O (3 mL) was added to the residue, which was then extracted with EtOAc (3 × 6 mL). The organic layer was washed with H_2O (3 mL) and brine (3 mL), dried (Na_2SO_4), filtered, and and the solvent was removed under reduced

pressure to give the colorless oil, which was directly dissolved in CH_2Cl_2 (4 mL), and TFA (2 mL) was added. The mixture was stirred for 4 h at 0 °C. Then, the solvent was removed in vacuum to give the crude product **1**, which was dissolved in pyridine (2 mL) and Ac_2O (1 mL) containing a catalytic amount of DMAP. The mixture was stirred at r.t. for 24 h. The reaction mixture was diluted with EtOAc (10 mL) and washed with sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, and filtered. Concentration of the filtrate followed by chromatography gave pentaacetate **11** (23 mg, 68% over 3 steps) as a white solid; mp 91–93 °C; $[\alpha]_D^{20}$ +20.0 (*c* 0.075, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (s, 6 H), 2.06 (s, 3 H), 2.07 (s, 6 H), 4.39 and 4.64 (ABq, *J* = 13.2 Hz, 2 H), 5.02–5.11 (m, 2 H), 5.36 (br d, *J* = 6.8 Hz, 1 H), 5.45 (dd, *J* = 10.0, 6.4 Hz, 1 H), 5.70 (br d, *J* = 8.4 Hz, 1 H), 5.89 (dd, *J* = 5.2, 1.2 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 20.8, 20.8, 20.8, 23.3, 44.9, 62.9, 68.5, 69.0, 71.2, 126.1, 134.3, 169.9, 170.0, 170.2, 170.3, 170.4. IR (film): 3363, 3269, 2924, 2850, 1743, 1649, 1556, 1469, 1371, 1223, 1024 cm^{-1}. MS (EI): *m/z* (%) = 385 (0.67) [M^+], 326 (100.00), 223 (57.20), 164 (68.60). HRMS (EI): *m/z* calcd for $C_{17}H_{23}NO_9$ [M^+]: 385.1373; found: 385.1370.

