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# Total synthesis of A-315675 based on the cascade Overman rearrangement

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**Abstract**

The chiral and stereoselective total synthesis of A-315675 **1**, an antiinfluenza agent, is described. The vicinal diamino moiety in **1** was stereoselectively constructed by the cascade Overman rearrangement of a vicinal allylic-homoallylic diol derived from D-tartrate.


*Keywords:* A-315675; Antiinfluenza agent; Total synthesis; Cascade Overman rearrangement

A-315675 **1** is an antiinfluenza agent developed by the Abbott scientists and has been reported to show a high inhibitory activity against neuraminidases.[1] The unique structure of **1**, a highly functionalized pyrrolidine core with a *cis*-propenyl group as well as four contiguous stereogenic centers including a vicinal diamino moiety and a tertiary ether function, is reported to be crucial for its biological activity, and has offered synthetic challenges. To date, three chiral syntheses of **1** have appeared. In 2002, the Abbott group reported the chiral synthesis of **1**, in which the vicinal diamino function was constructed by the stereoselective condensation of a chiral imine, derived from (2*E*)-2-methylpent-2-en-1-ol by Sharpless asymmetric epoxidation, with a siloxypyrrole to give the α,β-unsaturated γ-lactam possessing the vicinal diamino function. After introduction of the *cis*-propenyl group by the conjugate addition of *cis*-1-propenylcuprate, the carboxyl group at C-2 was created by the reaction of an *N*-acyliminium intermediate with TMSCN, followed by hydrolysis.[2] The total synthesis of **1** reported from the Hanessian group in 2002[3] employed the stereocontrolled addition of a propiolate ester to a chiral nitrone derived from D-serine for the construction of the vicinal diamino moiety. After chemo- and stereoselective reduction of the carbon–carbon triple bond, the *N*-hydroxy group was reduced to afford an α,β-unsaturated γ-lactam, which was transformed into **1** by a method similar to that developed by the Abbott group. In 2003, the Abbott group reported the improved and practical synthesis of **1** utilizing the enzymatic resolution of methyl 2-methoxy-2-methyl-pentanoate.[4]

In this Letter, we report the chiral and stereoselective total synthesis of A-315675 **1** starting from D-tartrate, in which the vicinal diamino function was effectively generated by the cascade Overman rearrangement of a vicinal allylic-homoallylic diol, and the pyrrolidine ring was constructed by the lactam formation of a 4,5-diaminocarboxylic acid derivative.

Our retrosynthetic analysis, taking into account the successful precedents of the total synthesis, suggested that γ-lactam **2**, which had been reported as the synthetic intermediate in the total synthesis of **1** by the Hanessian group[3] and the Abbott group,[4] would be a suitable target compound (Fig. 1). Lactam **2** was expected to be prepared from acyclic 4,5-diamino-carboxylic acid derivative **3**, whose acetic acid moiety ($-CH_2CO_2H$) was envisioned to be introduced by Claisen rearrangement of allylic alcohol **4** using triethyl orthoacetate. For the stereoselective construction of the vicinal diamino structure in **4**, the cascade Overman

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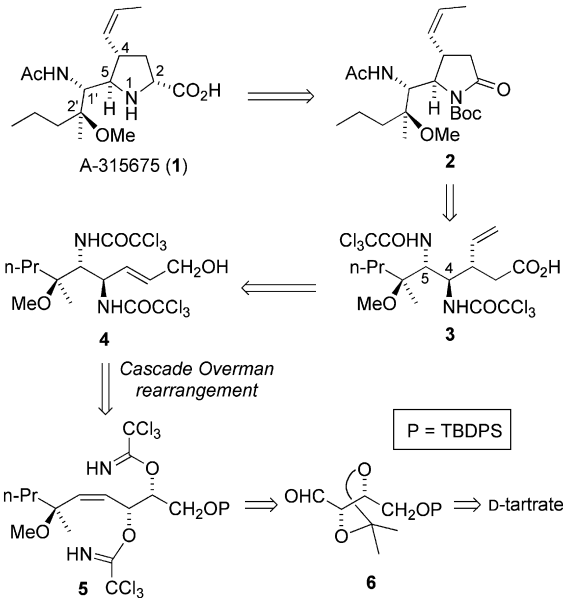
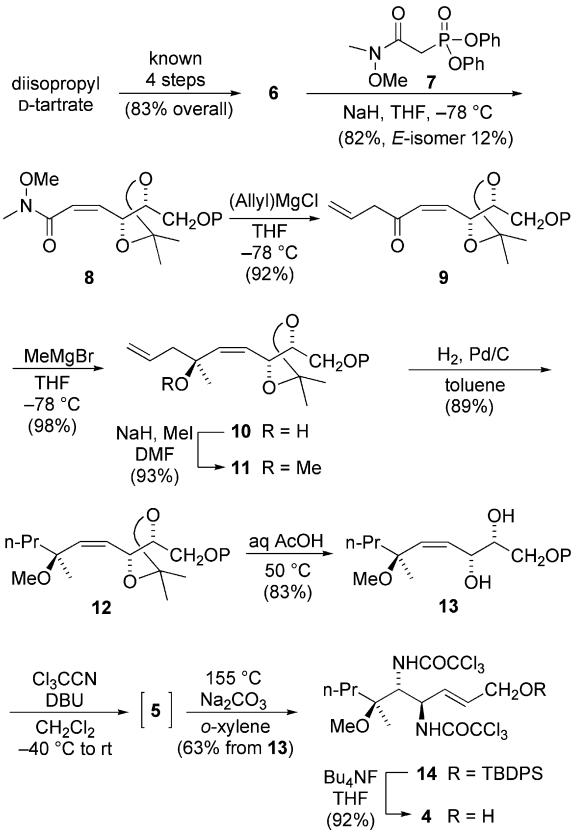



Fig. 1. Structure of A-315675 and its retrosynthetic analysis. TBDPS = –$SiPh_2$(*t*-Bu), Boc = –C(O)O(*t*-Bu).




Scheme 1. P = TBDPS [–Si(*t*-Bu)$Ph_2$], allyl = $CH_2$=CH–$CH_2$–.

rearrangement of bis-trichloroacetimidate possessing *Z*-olefin **5** was planned. It is known that the Overman rearrangement is a suprafacial [3,3]-sigmatropic reaction and the rearrangement of a chiral secondary imidate gives the corresponding trichloroacetamide with transfer of chirality via the chair-like transition structure.[5] If the cascade Overman rearrangement of **5** works as expected, the diamino function could be constructed in a one-step reaction, and the two C–O stereochemistries in the starting material **5** would be effectively transferred to the C–N stereogenic centers in **4** by the sequential chirality transfer. Although several examples of the stereoselective C–N bond formation via the chirality transfer utilizing the Overman rearrangement and related sigmatropic rearrangements on secondary allylic alcohols have been reported,[5,6] its cascade versions have received little attention.[7] The bis-trichloroacetimidate derivative **5**, in turn, was envisioned to be derived from aldehyde **6**, which would be readily prepared from D-tartrate.[8]

The *Z*-selective Horner–Wadsworth–Emmons olefination of the known aldehyde **6**,[8] prepared from diisopropyl D-tartrate in four steps with an 83% overall yield, with Ando-type reagent **7**[9] gave *Z*-olefin **8**[10] and its *E*-isomer in 82% and 12% isolated yields, respectively (Scheme 1). The treatment of **8** with allylmagnesium chloride afforded ketone **9** (92%), whose reaction with methylmagnesium bromide at −78 °C proceeded with a high stereoselectivity to provide tertiary alcohol **10** as a single isomer in 98% yield. The chelation of magnesium between the ketone carbonyl and the oxygen in the dioxolane ring would be responsible for the observed high stereoselectivity.[11] Etherification of the tertiary alcohol in **10** gave **11** (93% yield), whose hydrogenation in the presence of Pd on carbon selectively reduced the sterically unhindered terminal alkene to give **12** in 89% yield. Removal of the acetonide group in **12** provided the precursor of the cascade Overman rearrangement, vicinal allylic-homoallylic diol **13**, in 83% yield. The treatment of **13** with trichloroacetonitrile in the presence of DBU afforded the bis-imidate **5**. When the bis-imidate **5** was heated at 155 °C in *o*-xylene in the presence of $Na_2CO_3$[12] in a sealed tube, the crucial cascade Overman rearrangement successfully took place to provide diamide **14** as a single isomer in 63% yield from **13**. Although the structure of **14** could not be fully determined by spectroscopic methods at this stage, the successful conversion of **14** into the Hanessian's intermediate **2** (vide infra), whose structure has been unambiguously determined by an X-ray analysis,[3] confirmed the assigned structure.

In the first Overman rearrangement of **5**, there would be two plausible chair-like transition structures,[5] TS-a and TS-b (Fig. 2). In TS-b which gives rise to an epimeric rearranged product with a *Z*-olefin **5″**, the bulky substituent (–CH(OCNHCCl$_3$)$CH_2$OTBDPS) is in the disfavored axial position, and there would be severe non-bonded interactions between the axial substituent and a substituent in the *Z*-olefin. Due to these sterically disfavored interactions in TS-b, the transition structure TS-a would become a more favored one, thus affording the first rearranged product **5′** exclusively. Further rearrangement of **5′** via a similar chair-like transition structure to TS-a stereoselectively afforded doubly rearranged product **14**. It is noteworthy

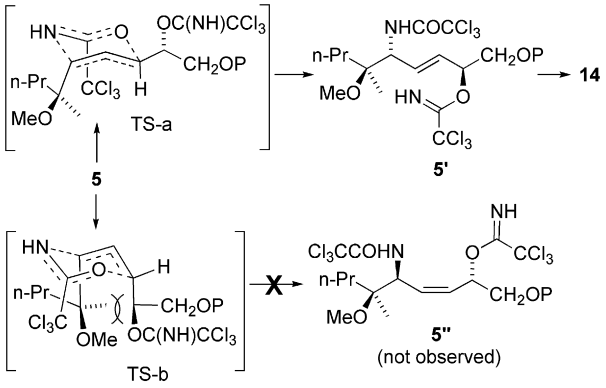
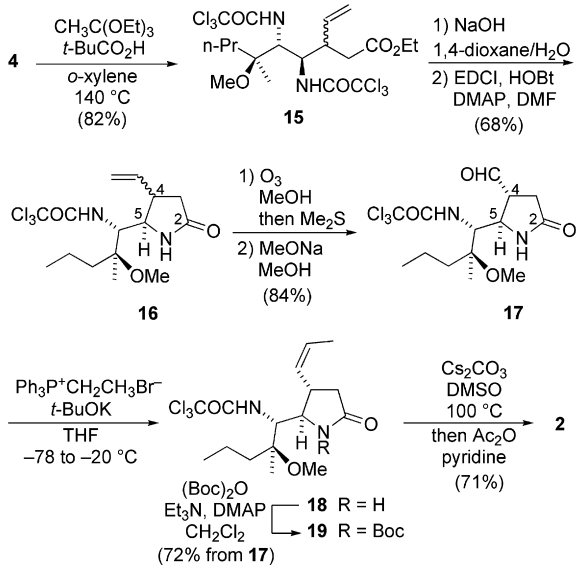



Fig. 2. The plausible transition structures of Overman rearrangement of **5**.

that in spite of the considerable steric hindrance in **5** due to the presence of the *Z*-olefin as well as the adjacent tertiary ether, the cascade rearrangement smoothly proceeded in a concerted manner to generate the 1,2-diamido function in a one-step reaction with complete chirality transfer. To introduce the acetate unit to **14**, the silyl protecting group was removed to give **4** (92% yield).

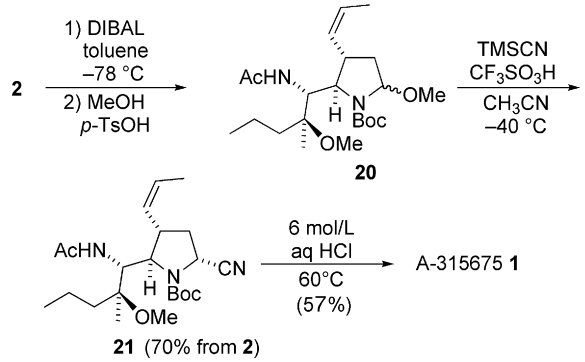
The Johnson–Claisen rearrangement of **4** in triethyl orthoacetate in the presence of a catalytic amount of pivalic acid as the acid catalyst at 140 °C afforded **15** as a diastereomeric mixture (1:3) in 82% yield (Scheme 2). The hydrolysis of the ethyl ester function in **15** with aqueous NaOH provided the carboxylic acid, which was then treated with EDCI and HOBt in the presence of DMAP to give γ-lactam **16** as a diastereomeric mixture (1:3) in 68% yield from **15**. The trichloroacetyl group on the nitrogen in the lactam ring was selectively removed under the stated reaction conditions. At this stage, the diastereoisomers were cleanly separated and the $^1$H NMR analyses of the products revealed that the major product was the 4,5-cis isomer, whereas the minor one was the 4,5-trans isomer. Ozonolysis of **16** (1:3 diastereomeric mixture) followed by reductive workup gave the diastereomeric aldehydes, which was subject to the base-induced epimerization at C-4 to provide aldehyde **17** possessing a 4,5-trans stereochemistry as a single isomer in 84% yield from **16**. Wittig reaction of **17** with the ylide generated from ethyltriphenylphosphonium bromide with *t*-BuOK[13] at −20 °C proceeded in a highly *Z*-selective manner and afforded **18**. The *E*-isomer of **18** could not be detected in the reaction mixture by the $^1$H NMR analysis.[14] The treatment of **18** with $Boc_2O$ in the presence of triethylamine and DMAP gave *N*-Boc γ-lactam **19** in 72% yield from **17**. The *N*-trichloroacetyl group in **19** was deprotected by the action of $Cs_2CO_3$ in DMSO,[15] and the corresponding amine was acetylated to provide **2**, which is known as the synthetic intermediate of A-315675,[3,4] in 71% yield. The $^1$H and $^{13}$C NMR data of **2** were totally identical to those reported by the Hanessian group.[3]




Scheme 2. EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodimide hydrochloride, HOBt = 1-hydroxybenzotriazole, DMAP = 4-dimethylaminopyridine.

Finally, according to the reported procedure by the Abbott[2,4] and Hanessian[3] groups, compound **2** was transformed into A-315675 **1** in a four-step reaction sequence as shown in Scheme 3. Thus, the reduction of the lactam carbonyl in **2** with DIBAL followed by treatment with MeOH and *p*-TsOH gave aminal **20** as an anomeric mixture (ca. 1:1). Introduction of a cyano group into **20** by the reaction with TMSCN in the presence of $CF_3SO_3H$ followed by chromatographic separation afforded **21** as a single isomer in 70% yield from **2**. Acid hydrolysis of **21** followed by purification with the reversed phase (Wakogel 50C18) and ion exchange (Amberlite IR 120B, $H^+$ form) chromatographies furnished **1** in 57% yield. The spectral data ($^1$H and $^{13}$C NMR) as well as the $[\alpha]_D$ value of synthetic **1** {$[\alpha]_D^{19}$ −47.7 (*c* 0.44, $H_2O$)} showed good agreement with those reported for A-315675 by the Abbott group {$[\alpha]_D$ −50.2 (*c* 0.25, $H_2O$)}.[2]

In summary, a new synthetic route to A-315675 starting from D-tartrate has been established. This stereoselective synthesis demonstrated that the cascade Overman rearrangement is highly effective for the stereoselective one-step construction of the vicinal diamino functionality with chirality transfer. Stereoselective generation of the tertiary




Scheme 3. DIBAL = diisobutylaluminum hydride, TMS = –$SiMe_3$.

alcohol under chelation control is also noteworthy. Since vicinal diamino structures are frequently found in biologically significant natural products as well as chiral ligands for asymmetric catalysts, the methodology developed in this study, that is, the cascade Overman rearrangement of vicinal allylic–homoallylic alcohols, would be applicable to the preparation of such important compounds. Further study regarding the synthesis of natural products based on the methodology employing the cascade sigmatropic rearrangement[16,17] is now underway.

## Supplementary data

The spectrum data and $^{1}H$ and $^{13}C$ NMR spectra of compounds **9**, **10**, **12**–**14**, **4**, **15**, **17**, **19**, **2**, and **1** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.080.

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