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First total synthesis of (+)-viroallosecurinine

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Abstract—The first diastereoselective chiral synthesis of (+)-viroallosecurinine, isolated from *Securinega virosa* as a cytotoxic alkaloid, was achieved by using a chelation-controlled addition of an alkyne moiety to the corresponding ketone, and a ring-closing metathesis, as key reactions.

(+)-Viroallosecurinine **1** was isolated from the leaves of *Securinega virosa*,[1] *Phyllanthus discoideus*,[2] and *Breynia coronate*[3] as a cytotoxic alkaloid together with its diastereoisomeric alkaloid, securinine **2**, and their antipodal forms, allosecurinine **3** and virosecurinine **4** (Fig. 1). Viroallosecurinine **1** exhibited a MIC of 0.48 μg/mL for *Pseudomonas aeruginosa* and *Staphylococcus aureus*; therefore, it was recognized to be a bactericidal since the yields of MIC/MBC were less than 1.[4] This alkaloid also showed significant cytotoxicity with ED_{50} value of 0.9 μg/mL in in vitro P-338 tissue culture cell.[5]

Recently, we have succeeded in the diastereoselective synthesis of (−)-securinine **2** by using a tandem ring-closing metathesis (RCM)[6] of a dienyne derivative[7] as a key step, as shown in Scheme 1, where the diastereoselective construction of the tertiary alcohol, a crucial step in the synthesis, was achieved by introduction of the alkyne moiety to the *N*-Boc protected ketone via the

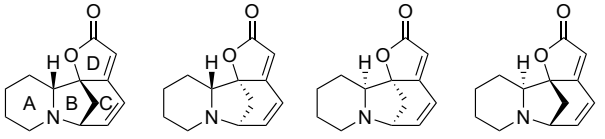
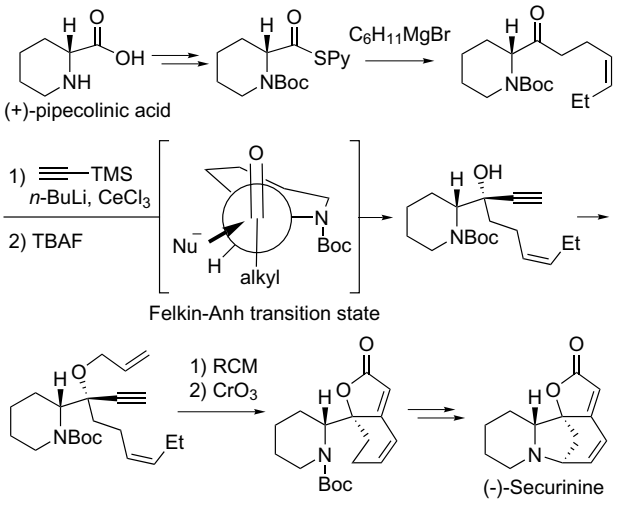


Figure 1. *Securinega* alkaloids.



Scheme 1. Synthesis (−)-securinine via tandem RCM reaction.

Felkin–Anh transition state.[8] Although we also succeeded in the stereoselective construction of the A, C, and D rings of viroallosecurinine by using the same strategy in the previous paper,[8] its further conversion to viroallosecurinine resulted in failure, since the difficulties were encountered in the selective hydrolysis of the *N*-acetyl group of the piperidine ring.

Since we could establish a facile synthetic path to *Securinega* alkaloids by using a tandem RCM of the dienyne system, we further applied this methodology to the first total synthesis of viroallosecurinine.

In order to accomplish the synthesis of viroallosecurinine **1**, a use of a labile *N*-protecting group, such as Boc

Keywords: (+)-Viroallosecurinine; Ring closing-metathesis; Chelation-controlled addition; *Securinega* alkaloid; Diastereoselective total synthesis.

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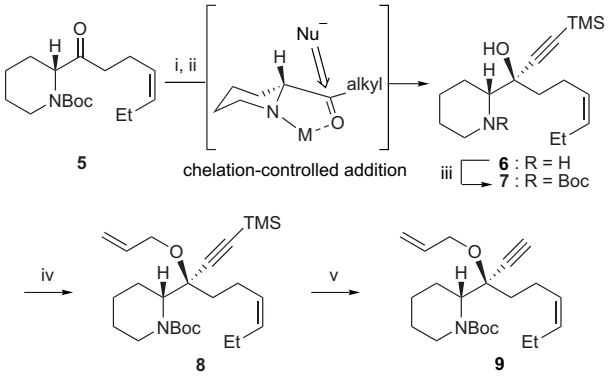
group, and introduction of an alkyne moiety to the ketone **5** with the opposite stereoselectivity to the case of the synthesis of securinine would be required. Since such stereoselective introduction would be achieved via a chelation transition state by employing the corresponding NH compound as the starting material,[9] we started to prepare the key starting material as follows.

N-Boc group of the optically active ketone **5**,[8] prepared from (+)-pipecolinic acid, was deprotected to give the amino ketone, which, on treatment with 2 equivalents of lithium trimethylsilylacetylide in the presence of cerium(III) chloride in THF gave the desired *tert*-alcohol **6**.[10] The alcohol **6** was then converted to its *N*-Boc derivative by treatment of the secondary amine with $(Boc)_2O$ under basic condition to give the corresponding tertiary alcohol **7** in 73% yield for three steps together with its diastereoisomer in 6% yield, respectively.

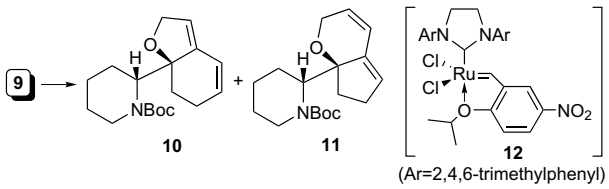
The observed stereoselectivity was rationalized by assuming that the addition would proceed via the chelation transition state as depicted in Scheme 2. When this reaction was carried out in the absence of cerium(III) chloride, partial racemization was observed.[11]

Although *O*-allylation under the acidic condition employing allyl trichloroacetimidate and triflic acid afforded the desired product, the reaction was found to be insufficient in terms of the conversion yield and also its reproducibility. Finally, we were able to find the optimal reaction conditions, fortunately, where the tertiary alcohol **7** was treated with allyl *tert*-butylcarbonate and triphenylphosphine in the presence of the palladium catalyst[12] to provide the desired allyl ether **8** in satisfactory yield.

After deprotection of the trimethylsilyl group, the resulting dienyne **9** was subjected to a tandem RCM reaction using 1 mol% loading of the nitro-derivative of Hoveyda catalyst **12**[13] in methylene chloride to give the cyclization product **10** having a 7-oxabicyclo[4.3.0]nona-2,9-diene system corresponding to the C and D rings of



Scheme 2. Reagents and conditions: (i) trifluoroacetic acid, CH_2Cl_2, 0 °C; (ii) *n*-BuLi, trimethylsilylacetylene, $CeCl_3$, THF, −78 °C; (iii) $(Boc)_2O$, K_2CO_3, dioxane/H_2O (4:5), rt (73% from **5** and 6% for diastereomer of **7**); (iv) $Pd_2(dba)_3$, PPh_3, allyl *t*-butylcarbonate, THF 65 °C (90%); (v) TBAF, THF, 0 °C (97%).

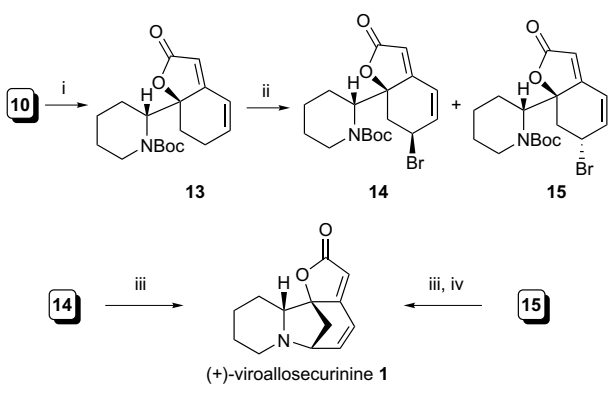


Scheme 3. Reagents and conditions: 1 mol% of **12**, CH_2Cl_2, rt (80% for **10** and 20% for **11**).

the target compound, in addition to another cyclization product **11** in 20% yield (Scheme 3).

Allylic oxidation of the major cyclization product **10** with CrO_3 in the presence of 3,5-dimethylpyrazole[14] afforded the γ-lactone **13** in 75% yield. In order to accomplish the total synthesis of viroallosecurinine **1**, the lactone **13** was treated with *N*-bromosuccinimide and AIBN in CCl_4 to give two allylic bromides **14** and **15** in a ratio of ca. 4:3. Although the stereochemistries of the bromides were not determined at this stage, those two bromides were thought to be diastereoisomeric compounds based on the analyses of their spectroscopic data. Treatment of one of the diastereoisomers **14** with trifluoroacetic acid at room temperature gave viroallosecurinine in 78% yield, under such mild reaction conditions. These results indicated that the bromine in **14** was introduced with *S*-configuration, so that the attack of the secondary amine, after removal of the protecting group, occurred simultaneously from the backside of the bromide smoothly through a S_N2 reaction mechanism to give the desired product, whereas the cyclization of another diastereoisomeric bromide **15**, after deprotection of the *N*-Boc group with trifluoroacetic acid, by treatment with K_2CO_3 in THF was found to be sluggish affording the desired product in 19% yield (Scheme 4).

In this case, the cyclization might proceed through an S_N1-like reaction mechanism to give the desired product, though the yield was very low. Thus, the solvent was changed from THF to the polar aprotic solvent DMF. Fortunately, the cyclization took place in 87% yield for 2 steps to provide (+)-viroallosecurinine **1**. The specific



Scheme 4. Reagents and conditions: (i) $CrCO_3$, 3,5,-dimethylpyrazole, CH_2Cl_2, −20 °C (75%); (ii) *N*-bromosuccinimide, AlBN, CCl_4, reflux (44% for **14** and 35% for **15**); (iii) trifluoroacetic acid, rt (78%); (iv) K_2CO_3, DMF, rt (87% from **15**).

optical rotation of the synthesized compound **1** {$[\alpha]_D$ +1113 (*c* 1.00, EtOH), lit.,[1] $[\alpha]_D$ +1085 (EtOH), lit.,[2] $[\alpha]_D$ +990 (*c* 0.98, EtOH)} and its spectroscopic data[15] were in agreement with those reported.

In summary, we were able to establish the first diastereoselective chiral synthesis of viroallosecurinine **1** by employing a tandem RCM of the dienyne system as a key reaction. In this synthesis, we found that the intramolecular cyclization of allyl bromide took place either through a S_N2 and/or S_N1 reaction mechanism depending on the reaction conditions employed. This methodology is obviously applicable to the synthesis of other *Securinega* alkaloids, such as norsecurinine and so on.

Acknowledgements

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10. The stereochemistry of the product was determined by its transformation into the final compound.
11. When this reaction was carried out in the absence of cerium chloride, the optical rotation of the product was $[\alpha]_D$ +68.4 (*c* 1.00, $CHCl_3$). On the other hand, the pure compound has $[\alpha]_D$ +87.9 (*c* 1.00, $CHCl_3$).
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15. Selected data for **1**: mp 145–147 °C (pale yellow needle, recrystallized from hexane–acetone); $[\alpha]_D$ +1113 (*c* 1.0, EtOH). ^{1}H NMR ($CDCl_3$) δ 1.07–1.50 (3H, m), 1.62–1.75 (3H, m), 1.93 (1H, d, $J = 9.7$ Hz), 2.69 (1H, dd, $J = 4.3$, 9.7 Hz), 2.74–2.78 (2H, m), 3.67 (1H, dd, $J = 3.3$, 13.0 Hz), 3.91 (1H, dd, $J = 4.6$, 4.8 Hz), 5.73 (1H, s), 6.65 (1H, d, $J = 9.1$ Hz), 6.82 (1H, dd, $J = 5.3$, 9.1 Hz); ^{13}C NMR ($CDCl_3$) δ 18.4, 21.0, 22.1, 42.6, 43.6, 58.8, 60.7, 91.7, 109.0, 122.7, 148.6, 167.4, 172.8; IR (thin film) 1756, 1632, 1460, 1448, 1375, 1318, 1292, 1260, 1178, 1118, 1096, 1077, 960, 908, 802 cm^{-1}; HRMS *m*/*z* found: 217.1100 (calcd for $C_{13}H_{15}NO_2$: 217.1103).