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Total Synthesis of (−)-Secu'amamine A Exploiting Type II Anion Relay Chemistry

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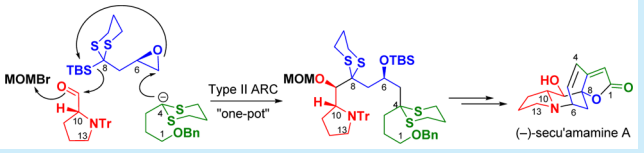
Supporting Information

ABSTRACT: A total synthesis of (−)-secu'amamine A has been achieved exploiting Type II Anion Relay Chemistry (ARC) to provide the full linear carbon and nitrogen skeleton in a single flask with the requisite stereochemistry and functionality. A mechanistic rationale is also proposed to account for the stereochemical outcome of the key aldol reaction leading to the advanced aza tricyclic core.



The Securinega alkaloids (Figure 1) comprise biolgically active, architecturally intricate natural products, isolated from the Securinga and Phyllanthus plant species.[1] The most abundant of these, (−)-securinine (**1**), was first reported in 1956.[2] Since that time approximately 30 congeners have been reported. Given the wide range of biological activities,[1b] including antimalarial,[3] antibacterial,[4] cytotoxicity,[5] and GABA receptor antagonistic activity,[6] in conjunction with their challenging structural features that include a compact tetracyclic core, possessing an $\alpha,\beta,\gamma,\delta$-unsaturated bicyclic-$\gamma$-lactone motif, this class of natural products has attracted wide interest from both the chemical and biological communities.[7]

In 2003, a particularly intriguing member of this class, (−)-secu'amamine A (**4**),[8] was isolated by Osaki and co-workers from the leaves and twigs of Securinga suffruticosa va. Amamiensis that is endowed with a novel aza-bicyclo-[3,3,1]-nonane core. This structure led Magnus and Padilla to propose a novel biosynthetic pathway from 3β-hydroxyallosecurinnine, derived via oxidation of allosecurinnine (**3**), which in turn was suggested to undergo a rearangement via an aziridinium ion intermediate.[9] Notwithstanding the interesting chemistry and architecture, to date only one total synthesis of (−)-secu'amamine A (**4**) has been reported, that by Weinreb and co-workers in 2008.[10]

Continuing with the biosynthetic analysis, the Securinga alkaloids are postulated to arise from only two amino acids, lysine and tyrosine,[11] highlighting Nature's ability to generate complexity from simple building blocks. In an attempt to mimic Nature's elegant biosynthesis of diverse molecular structures, we introduced and validated a series of multicomponent union tactics, termed Anion Relay Chemistry (ARC; Type I and II),[12] utilizing a bifunctional linchpin, as effective protocols to access molecular complexity in rapid fashion (Scheme 1).

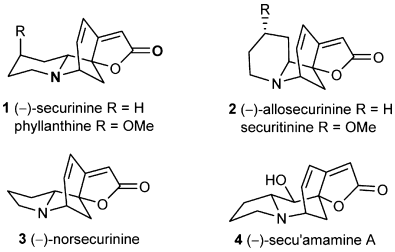
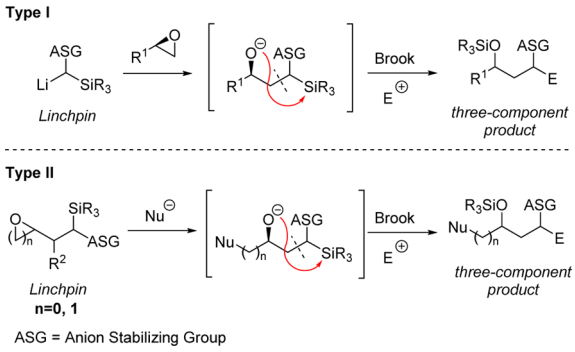


Figure 1. Securinega alkaloids.

Scheme 1. Type I and Type II Anion Relay Chemistry



We subsequently demonstrated the potential of the two ARC tactics with the synthesis of a series of biologically important natural products,[13] for example early studies on the construction of two frog alkaloids[12e−g] utilizing the Type I tactic, and more recently in Diversity Oriented Synthesis[14] with an effective, general protocol for the construction of all stereoisomers of a 2,4,6-trisubstituted piperidine library.[12g] Herein, we illustrate application of the ARC Type II multicomponent union tactic with a total synthesis of (−)-secu'amamine A (**4**).

For (−)-secu'amamine A (**4**; Scheme 2), we envisioned the critical diene motif to be constructed as reported in the Weinreb synthesis from advanced tetracyclic intermediate **5**,[10] obtained by oxidation of diol **6**. In turn, indolizidine **7**, anticipated to exist

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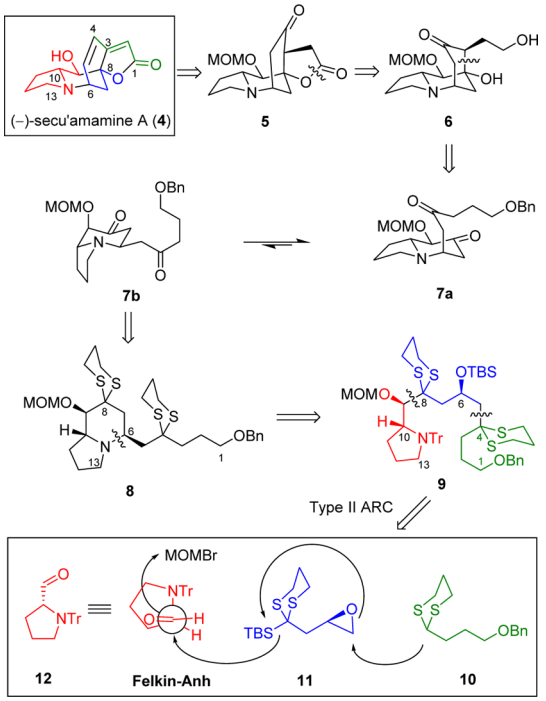
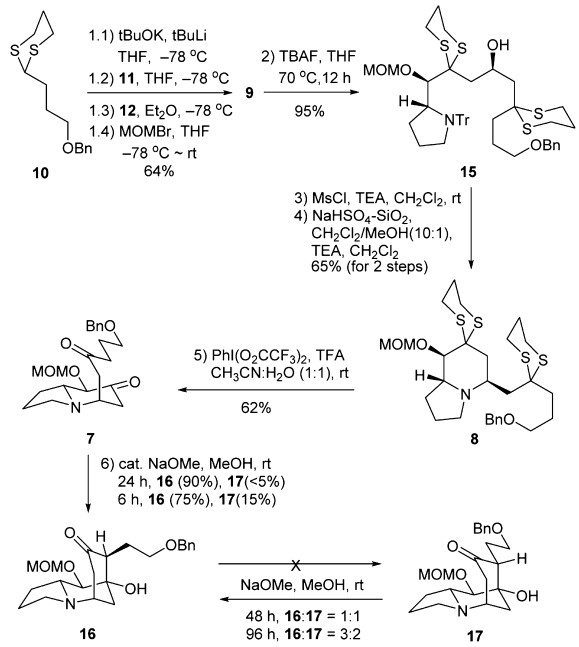
Scheme 2. Retrosynthesis of (−)-Secu'amamine A



Scheme 3. Synthesis of Azabicyclo-[3,3,1]-nonane Core



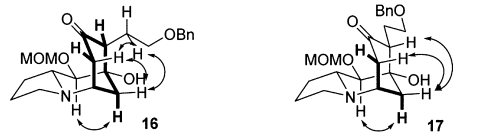
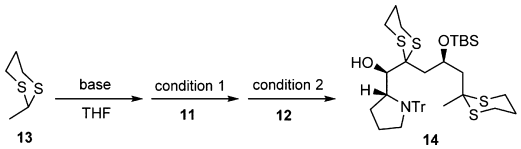


Figure 2. NOE and $^4J_{ee}$-couplings.

predominantly as **7a**, would permit intramolecular aldol cyclization to furnish the rigid aza-bicyclo-[3,3,1]-nonane core of **6**. The stereochemical outcome of this intramolecular aldol would prove critical for this synthetic venture (*vide infra*). In turn to access indolizidine **8**, we planned to employ S_N2 intramolecular bond construction with the pyrrolidine nitrogen in **9** and an activated C6 carbon−oxygen bond after removal of the TBS and Tr groups. Finally and central to the synthesis, we would call on the Type II ARC tactic to showcase the union of four components (i.e., the dithiane anion derived from **10**, linchpin **11**, aldehyde **12**,[15] and MOMBr) to construct *in a single flask* the complete carbon and nitrogen linear backbone (**9**) of (−)-secu'amamine A (**4**) with the requisite functionality and stereochemistry[16] to complete the synthetic venture.

We began with the study of the Type II ARC tactic to develop optimal conditions to generate the model three-component adduct **14** (Table 1) with the expectation that the MOM group might be added as a last step to furnish the 4-component adduct **9**. To optimize the requisite Brook rearrangement process, previously demonstrated to be enhanced by alternating temperature, countercation, and/or solvent polarity,[12a] we focused first on temperature. After extensive experimentation, we discovered that the maximum yield of the Brook rearrangement product that could be achieved was ca. 50% employing THF−Et_2O with temperature modulation from −78 to 0 °C over 1 h (Table 1, entries 1 and 2). Next, we changed the solvent polarity (i.e., addition of HMPA) to trigger the Brook rearrangement. Unfortunately addition of the requisite dithiane anion derived via Brook rearrangement to aldehyde **12** in the presence of

Table 1. Optimizing Multicomponent Reaction



entry	base	condition 1	condition 2	yield (%)
1	*n*-BuLi	THF, −78 to −10 °C, 1 h	Et_2O, −78−0 °C, 2 h	20
2		THF/Et_2O (1:2), −78−0 °C, 1.5 h		50
3		Et_2O/HMPA[a]		<10
4	*t*-BuOK, *n*-BuLi	THF, −78 °C, 0.5 h	normal addition[c]	15
5		THF/Et_2O (1:5), −78 °C, 0.5 h[b]	reverse addition[d]	30
6			normal addition[d]	75
7				45[e]

[a]**11** in Et_2O, −30 °C, 20 min; HMPA/Et_2O, −78 °C. [b]**11** in THF, −78 °C, 0.5 h, then diluted with Et_2O (THF/Et_2O = 1:5). [c]**12** in THF, −78−0 °C 2 h. [d]**12** in Et_2O/THF (5:1), − 78−0 °C, 2 h. [e]0.5 equiv, *t*-BuOK.

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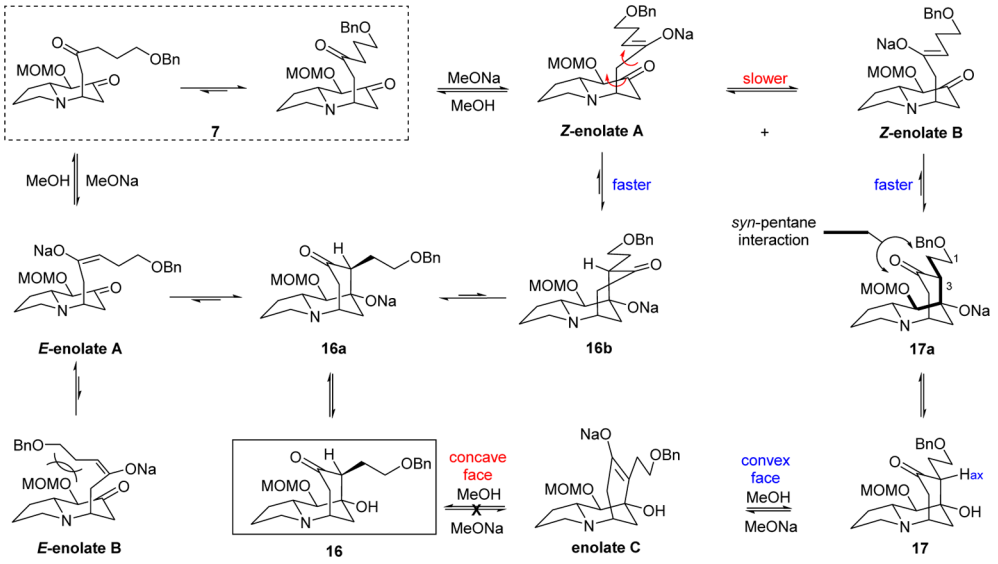
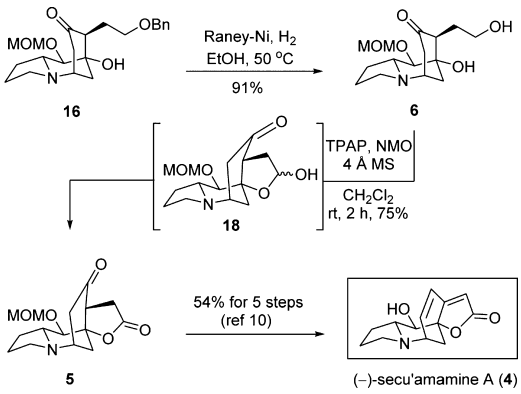
Scheme 4. A Plausible Mechanism for the Conversion of 7 to 16 and 17 and Isomerization



Scheme 5. γ-Lactone Formation



HMPA proceeded with low conversion (Table 1, entry 3). We turn next to different countercations to trigger the Brook rearrangement. Here we discovered viable conditions involving the deprotonation/Brook rearrangement sequence by employing the Schlosser base (i.e., K^+; Table 1, entry 4). Addition of the Brook derived dithiane anion to aldehyde **12**, however, initially resulted in extensive quenching by the acidic α aldehydic proton, which we reason was attributable to the 1 equiv of *t*-BuOLi/*t*-BuOK in the reaction. Quenching of the dithiane anion could however be significantly reduced by diluting the reaction mixture with ether (5-fold relative to THF), before addition of aldehyde **12**, thereby precipitating *t*-BuOLi/*t*-BuOK at −78 °C (Table 1, entry 6). Attempts to reduce the amount of *t*-BuOK (0.5 equiv) did not improve the conversion (Table 1, entry 7).

Exploiting the optimized conditions, the four-component adduct **9** (Scheme 3) could now be generated in a single flask by capturing the alkoxide derived from the sequential addition of dithiane anion **10**, linchpin **11**, and aldehyde **12** with MOMBr. The yield for the overall reaction sequence was 64%. The TBS group was next removed with TBAF in THF at reflux, to furnish alcohol **15**. Mesylation of the sterically hindered secondary hydroxyl group in **15** was then successfully achieved with 1.5 equiv of MsCl and excess triethylamine. Turning to removal of the trityl group, difficulties were initially encountered due to elimination of the mesylate. Fortunately, we discovered that use of mild acidic heterogeneous conditions ($NaHSO_4$−SiO_2 in CH_2Cl_2/MeOH)[17] provided the requisite pyrrolidine salt, which in turn could be treated with triethylamine in a dilute solution[18] of CH_2Cl_2 to form indolizidine **8**. It is noteworthy that cyclization to **8** was achieved without purification after removal of inorganic salts via simple filtration (two steps, 65% yield).

Continuing with the synthesis, removal of the dithianes employing the Fleming protocol[19] led to dione **7**. Attempts to achieve the critical intramolecular aldol reaction (e.g., **7** → **16**), initially employing LDA or KHMDS, generated a complex mixture with the desired aldol **16** produced only as a minor product. Considerable experimentation however eventually led to the discovery that cyclization to form azabicyclo-[3.3.1]-nonane **16** could be achieved in high yield employing a catalytic amount of sodium methoxide in anhydrous methanol over a 24 h period with formation of a trace amount of the alternate aldol isomer **17**. We subsequently found that sufficient **17** for characterization could be isolated if the aldol reaction was ended after 6 h. During these studies, we also discovered that **17** undergoes slow isomerization to generate a mixture of **16** and **17**, whereas **16** is not converted to **17** in accordance with the result of Weinreb.[10] In each case the stereochemistry and conformational rigidity of **16** and **17** were assigned by observation of an NOE between the axial protons and a distinctive $^4J_{ee}$-coupling between the equatorial protons in the chair cyclohexanone core (Figure 2).

Based on the isomerization experiments, a mechanism for the cyclization of **7** and the isomerization process (**17** → **16**) can be proposed (Scheme 4). First, it is important to recognize that there are two possible *Z* and *E* enolate conformers. The observed and desired aldol **16** generated by reaction via **Z-enolate A** or ***E*-enolate A** is not expected to undergo subsequent enolization to generate **enolate C** given that the rigid tricyclic system **16** locks the equatorial proton at C3 at room temperature. On the other hand, the alternate minor aldol product **17**, derived from ***Z*-enolate B** but not from ***E*-enolate B**, given the strong steric interaction between MOM group and C1−2 side chain, can undergo either a retro-aldol reaction or enolization via abstraction of the axial proton at C3 to generate ***Z*-enolate B** and **enolate-C**, respectively, alleviating *syn*-pentane interactions between the MOM group and equatorial C1−2 side chain. Given

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the observed slow conversion of **17** to **16**, we postulate that the aldol reactions (**Z-enolate A** → **16a** and **Z-enolate B** → **17a**) are faster than both a retro-aldol reaction and the conformation change between *Z*-enolates **A** and **B** that requires rotation of the two bonds depicted in red. Correspondingly, interconversion via **enolate C** derived by abstraction of the axial proton at C3 in **17**, followed by protonation on the unfavored concave face, would be slow. Hence we postulate the slow conversion of **17** to **16** via a retro aldol, conformation change, and aldol (**17a** →**Z-enolate B** → **Z-enolate A** → **16a**).

With **16** in hand, removal of the benzyl group in **16** (Scheme 5) with Raney-Ni, followed by Ley−Griffith oxidation[20] of the resulting primary alcohol, furnished the known Weinreb tetracyclic γ-lactone **5**,[10] after oxidation of the initially formed lactol **18**.

Completion of synthesis of (−)-secu'amamine A (**4**) was then achieved following the Weinreb five-step sequence involving conversion of the ketone in **5** to the alkene and introduction of the requisite unsaturation in the γ-lactone. The overall yield for this five-step sequence was 54% as reported by Weinreb.[10]

In summary, a convergent synthesis of (−)-secu'amamine A (**4**) has been achieved employing Type II Anion Relay Chemistry (ARC) which permits the construction of a four-component advanced intermediate in a single flask possessing the full linear carbon and nitrogen skeleton of the target with the requisite functionality. Also attractive is formation of the tetracyclic core possessing the bridge head quaternary center, achieved by intramolecular aldol reaction, and the one-step oxidative lactonization to furnish **5**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02018.

Experimental procedures and spectroscopic and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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