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

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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 biologically 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,3 including antimalarial,4 antibacterial,5 cytotoxicity,6 and GABA receptor antagonistic activity,7 in conjunction with their challenging structural features that include a compact tetracyclic core, possessing an α,β,γ,δ-unsaturated bicyclic-γ-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 var. 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 rearrangement 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). 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 alkaloids12e−g utilizing the Type I tactic, and more recently in Diversity Oriented Synthesis14 with an effective, general protocol for the construction of all stereoisomers of a 2,4,6-trisubstituted piperidine library.12b 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 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). 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 alkaloids12e−g utilizing the Type I tactic, and more recently in Diversity Oriented Synthesis14 with an effective, general protocol for the construction of all stereoisomers of a 2,4,6-trisubstituted piperidine library.12b Herein, we illustrate application of the ARC Type II multicomponent union tactic with a total synthesis of (−)-secu’amamine A (4).

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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, 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 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, counterion, and/or solvent polarity, 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*        |               | <10       |
| 4     | t-BuOK, n-BuLi | THF, −78 °C, 0.5 h | normal addition* | 15        |
| 5     |         | THF/Et_2O (1:5), −78−0 °C, 0.5 h | reverse addition* | 30        |
| 6     |         |                   | normal addition* | 75        |
| 7     |         |                   |               | 45*       |

*11 in Et_2O, −30 °C, 20 min; HMPA/Et_2O, −78 °C. **11 in THF, −78 °C, 0.5 h, then diluted with Et_2O (THF/Et_2O = 1:5). ***12 in THF, −78−0 °C 2 h. ****12 in Et_2O/THF (5:1), −78−0 °C, 2 h. *****0.5 equiv, t-BuOK.
Brook derived dithiane anion to aldehyde resulted in extensive quenching by the acidic ing the Schlosser base (i.e., K⁺; Table 1, entry 4). Addition of the deprotonation/Brook rearrangement sequence by employing.

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 trityl group, differ

Continuing with the synthesis, removal of the dithianes employing the Fleming protocol19 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. 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 distinctive4 Jee-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-aldo 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.

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 (NaHSO4–SiO2 in CH2Cl2/MeOH)17 provided the requisite pyrrolidine salt, which in turn could be treated with triethylamine in a dilute solution of CH2Cl2 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).

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the observed slow conversion of 17 to 16, we postulate that the aldol reactions ($Z$-enolate A $\rightarrow$ 16a and $Z$-enolate B $\rightarrow$ 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 unavored concave face, would be slow. Hence we postulate the slow conversion of 17 to 16 via a retro aldol, conformation change, and aldol (17a $\rightarrow$ $Z$-enolate B $\rightarrow$ $Z$-enolate A $\rightarrow$ 16a).

With 16 in hand, removal of the benzylic group in 16 (Scheme 5) with Raney-Ni, followed by Ley–Griffith oxidation of the resulting primary alcohol, furnished the known Weinreb tetracyclic $\gamma$-lactone $S$, after oxidation of the initially formed lactol 18.

Completion of synthesis of (−)-secu’amine 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 $\gamma$-lactone. The overall yield for this five-step sequence was 54% as reported by Weinreb.10

In summary, a convergent synthesis of (−)-secu’amine 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 S.

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**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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**REFERENCES**

(1) Reviews: (a) Snieckus, V. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. 14, pp 425–503. (b) Beutler, J. A.; Brubaker, A. N. *Drugs Future* 1987, 12, 937. (c) Bayon, P.; Busque, F.; Figueredo, M. *Targets Heterocycl. Syst.* 2005, 9, 281. (d) Weinreb, S. *M. Nat. Prod. Rep.* 2009, 26, 758.

(2) Murav’eva, V. I.; Ban’kovskii, A. I. *Dokl. Akad. Nauk SSSR* 1956, 110, 998.

(3) Weenen, H.; Nkunya, M. H. H.; Bray, D. H.; Mwasumbi, L. B.; Kinabo, L. S.; Kilimami, V. A.; Wijnberg, J. B. *Planta Med.* 1990, 56, 371.

(4) Mensah, J. L.; Lagarde, I.; Ceschin, C.; Michelb, G.; Gleye, J.; Fournste, I. J. *Ethnopharmacol.* 1990, 28, 129.

(5) Tatamats, H.; Morii, M.; Yang, T.-H.; Chang, J.-J.; Lee, T. T.-Y.; Lee, K.-H. *J. Pharm. Sci.* 1991, 80, 325.

(6) (a) Rognan, D.; Boulangter, T.; Hoffmann, R.; Vercauteran, D. P.; Andre, J.-M.; Durant, F.; Wemmuth, C.-G. *J. Med. Chem.* 1992, 35, 1969.

(7) (b) Galvez-Ruano, E.; Aprison, M. H.; Robertson, D. H.; Lipkowitz, K. B. *J. Neurosci. Res.* 1995, 42, 666.

(7) (a) Review: Chirkin, E.; Atakladian, W.; Porée, F.-H. *Alkaloids: Chemistry and Biology 2013*, 74, 1–120. (d) Dhudhsia, B.; Cooper, B. F. T.; Macdonald, C. L. B.; Thadani, A. N. *Chem. Commun.* 2009, 463.

(b) Meideros, M. R.; Wood, J. L. *Tetrahedron* 2010, 66, 4701. (c) Chen, J.-H.; Levine, S. R.; Buergler, J. F.; McMahan, T. C.; Meideros, M. R.; Wood, J. L. *Org. Lett.* 2012, 14, 4531. (d) Sathish Reddy, A.; Sridri, P. *Tetrahedron Lett.* 2013, 55, 5926. (e) Sampath, M.; Lee, P.-Y. B.; Loh, T.-P. *Chem. Sci.* 2011, 2, 1988. (f) Wei, H.; Qiao, C.; Liu, G.; Yang, Z.; Li, C.-C. *Angew. Chem.* 2013, 125, 648; *Angew. Chem., Int. Ed.* 2013, 52, 620.

(g) Elseolby, A. M.; Wespe, D. A.; Poore, T. J.; Snyder, S. A. *Angew. Chem., Int. Ed.* 2013, 52, 5789. (h) Ma, N.; Yao, Y.; Zhao, B.-X.; Wang, Y.; Ye, W.-C.; Jiang, S. *Chem. Commun.* 2014, 50, 9284. (i) Zheng, X.; Liu, J.; Ye, C.-X.; Wang, A.-E.; Huang, P.-Q. *J. Org. Chem.* 2015, 80, 1034.

(h) Ohsaki, A.; Ishiyama, H.; Yoneda, K.; Kobayashi, J. *Tetrahedron Lett.* 2003, 44, 3097.

(10) Magnus, P.; Padilla, A. I. *Org. Lett.* 2006, 8, 3569.

(10) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* 2008, 130, 7562.

(11) Parry, R. J. *Bioorg. Chem.* 1978, 7, 277.

(12) (a) Smith, A. B., III; Pitram, S. M.; Boldi, A. M.; Gaunt, J. M.; Stouggatatikis, C.; Moser, W. H. J. *Am. Chem. Soc.* 2003, 125, 14435.

(b) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* 2008, 5883.

(13) (c) Smith, A. B., III; Kim, W.-S.; Wuest, W. M. *Angew. Chem., Int. Ed.* 2008, 47, 7082. (d) Smith, A. B., III; Kim, W.-S.; Tong, R. *Org. Lett.* 2010, 12, 588. (e) Smith, A. B., III; Tong, R. *Org. Lett.* 2012, 14, 1260.

(f) Smith, A. B., III; Kim, W.-S.; Proc. Natl. Acad. Sci. U. S. A. 2011, 108, 6787. (g) Smith, A. B., III; Han, H.; Kim, W.-S. *Org. Lett.* 2011, 13, 3328.

(h) Smith, A. B., III; Tong, R.; Kim, W.-S.; Maio, W. A. *Angew. Chem., Int. Ed.* 2011, 50, 8904. (i) Sanchez, L.; Smith, A. B., III *Org. Lett.* 2012, 14, 6314.

(15) (a) Smith, A. B., III; Doughty, V. A.; Lin, Q.; Zhuang, L.; McBriar, M. D.; Boldi, A. M.; Moser, W. H.; Murase, N.; Nakayama, K.; Sobukawa, M. *Angew. Chem., Int. Ed.* 2001, 40, 191. (b) Smith, A. B., III; Lin, Q.; Doughty, V. A.; Zhuang, L.; McBriar, M. D.; Korns, J. K.; Brook, C. S.; Murase, N.; Nakayama, K. *Angew. Chem. Int. Ed.* 2001, 40, 196.

(16) (c) Smith, A. B., III; Kim, W.-S.; Fuertes, M. J. *Org. Lett.* 2003, 5, 2751.

(d) Smith, A. B., III; Kim, W.-S. *Org. Lett.* 2004, 6, 1493. (e) Smith, A. B., III; Kim, W.-S. *Org. Lett.* 2005, 7, 2327. (f) Smith, A. B., III; Kim, W.-S. *Org. Lett.* 2006, 7, 2547. (g) Wang, X.; Paxton, T. J.; Li, N.; Smith, A. B., III *Org. Lett.* 2012, 14, 3998. (h) Sokolsky, A.; Smith, A. B., III *Org. Lett.* 2012, 14, 4470. (i) Melillo, M.; Smith, A. B., III *Org. Lett.* 2013, 15, 2282. (j) Sokolsky, A.; Cattoen, M.; Smith, A. B., III *Org. Lett.* 2015, 17, 1898.

(18) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. J. *Chem., Soc., Chem. Commun.* 1987, 1625.