## A Flexible Strategy Based on a $C_2$ -Symmetric Pool of Chiral Substrates: Concise Synthesis of (+)-Valienamine, Key Intermediate of (+)- Pancratistatin, and Conduramines A-1 and E

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Received July 15, 2009





A new strategy invoking a new application of the [3,3] signatropic rearrangement of allylic azides and the presence of a  $C_2$  symmetry element within a pool of chiral substrates was evolved. Not only does this simple flexible strategy provide a concise approach to (+)-valienamine, but it also can readily be adopted for the synthesis of conduramines A-1 and E and the enantiopure azido carbonate 4, a key intermediate of (+)-pancratistatin.

Aminocyclitols and structurally related compounds constitute a continuing and growing class of important compounds for biological function.<sup>1</sup> The vast importance of the aminocyclitol unit valienamine **1**, which occurs widely as a central building block of pseudooligosaccharides and several complex aminoglycoside antibiotics,<sup>2</sup> has stimulated much synthetic activity and enhanced interest in simplifying their synthesis. Most reported total syntheses employ cyclitol quebrachitol,<sup>3</sup> D-glucose derivatives,<sup>4</sup> or (–)-quinic acid<sup>5a,b</sup> as the chiral building block, wherein new stereochemistries are introduced into compounds bearing preexisting ones. Such strategies are often limited by the need for lengthy protecting group manipulation and/or the use of relatively expensive chiral building blocks that are of limited availability. A noteworthy strategic exception is shown in the asymmetric symthesis of (+)-valienamine **1** reported by Trost, which uses Pd-catalyzed desymmetrization and *cis*-hydroxyamination.<sup>6</sup> In trying to devise a new convenient flexible strategy whereby the same readily available intermediate can be channeled into a different product by

LETTERS 2009 Vol. 11, No. 19 4278–4281

ORGANIC

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**Scheme 1.** Retrosynthesis of (+)-Valienamine, Conduramines A-1 and E, and a Key Intermediate of (+)-Pancratistatin



changing the reaction profile, we sought a concise and convergent approach, designed to afford easy access to both (+)-valienamine **1** and a variety of analogues. We chose cyclic diol **8**, readily prepared from  $C_2$ -symmetric L-tartaric acid,<sup>7</sup> as a versatile bridging intermediate en route to aminocyclitols and envisioned using azide to introduce amino group in the equivalent of a protected form (Scheme 1).

A key aspect of this new flexible strategy is the installation of the azido alcohol unit via the ring opening of the diol 8-derived allylic epoxide with an azide nucleophile with a complete control of regio- and stereochemistry.

Following the reported procedures (Scheme 2), the synthesis commenced with commercially available and cheap L-tartaric acid **5** or its derivative dimethyl 2,3-O-isopropylidenetartrate **6**. Reduction of **6** with DIBALH, followed by a highly diastereoselective divinylzinc addition to the in situ generated dialdehyde, afforded the desired vinyl carbinol **7**.<sup>7</sup> Subsequent RCM using the second generation Grubbs





catalyst afforded the corresponding cyclic diol **8**.<sup>7e</sup> Construction of allylic azide **10a** or **10b** called for a controlled introduction of an azido group. The high propensity of allylic azides to undergo [3,3] sigmatropic rearrangement<sup>8</sup> suggested that a simple route to both of the allylic azides **10a** and **10b** was potentially available. After considering a number of possibilities for installation of the azido alcohol unit with complete control of regio- and stereochemistry, we chose to use the in situ generated allylic epoxide **9** as a valuable key intermediate to allylic azides **10a** and **10b**. Gratifyingly, sequential addition of triflimide/sodium hydride and a solution of sodium azide in 1.5:1:1 DMF/EtOH/H<sub>2</sub>O at room temperature to cyclic vinyl carbinol **8** led to only the 1,2type azido alcohol **10a** in 66% yield. We surmise that this interesting transformation involves conversion of the diol to

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the pivotal allylic epoxide via base-promoted monotriflation of the hydroxyl group and intramolecular displacement by hydroxyl nucleophile and S<sub>N</sub>2 ring opening of the allylic epoxide at the allylic carbon with an azide ion with inversion of configuration. A significant advantages of this one-pot transformation is that no resolution steps are required and, because of the presence of a  $C_2$  symmetry axis within the diol 8 before monotriflation, there is no loss in yield due to the formation of diastereomers. On the other hand, performing this one-pot conversion process at reflux (~90 °C) smoothly redirects the reaction to the 1,4-type azido alcohol 10b (70%) with complete control of stereo- and regiochemistry. This result strongly implies that the less stable 1,2type azido alcohol would be initially formed and would then undergoes [3,3] sigmatropic rearrangement to provide the more stable 1,4-type azido alcohol 10b. Further evidence for this isomerization was obtained by heating allylic azide 10a in 1.5:1:1 DMF/EtOH/H<sub>2</sub>O at 90 °C and comparing the product to azide 10b. Molecular models reveal that this surprisingly high 1,4-type selectivity derives from effects of azido group orientation depicted in 10a and 10b. The difference between an axial and a pseudoequatorial environment of an azido group can lead to significant difference in the stability of 1,2- and 1,4-azido alcohols. Considering that intramolecular hydrogen bonding plays an important role in stabilizing the 1,2-azidocyclohexenol,<sup>8c</sup> this thermal isomerization of 1,2- to 1,4-type allylic azide represents a particularly intriguing success.

Both allylic azides 10a and 10b serve as valuable intermediates to approach aminocyclitols. Elaboration of 10a to (+)-valienamine 1 was initiated by oxidation of 10b with Dess-Martin periodinane, producing enone 11 (96%) (Scheme 3). The availability of 11 allowed for direct introduction of a hydroxymethyl group via the Baylis-Hillman reaction.<sup>9</sup> Treatment of **11** with formaldehyde solution (37% in  $H_2O$ ) in THF at room temperature followed by addition of imidazole (1.5 equiv) and aqueous NaHCO<sub>3</sub> (1 M) resulted in efficient formation of the desired hydroxymethylcyclohexenone 12 in 65% yield. Controlled reduction of enone 12 with NaBH<sub>4</sub> in methanol solution containing cerium chloride at -78 °C gave a 80% yield of alcohol 13 with excellent stereoselectivity (>16:1). Finally, reduction of azido alcohol 13 with LiAlH<sub>4</sub> followed by quenching with H<sub>2</sub>O/ HOAc provided (+)-valienamine 1, which was characterized as its tetraacetate 14 (50%). Comparison of the physical properties to those recorded confirms its identity.<sup>6</sup> This synthesis based on a  $C_2$ -symmetric pool of chiral substrates requires 8 steps from very cheap L-tartaric acid 5 to give (+)-valienamine in 8.4% overall yield. Another interesting synthetic application of 1,4-azido alcohol 10b is found in the one-pot transformation of 10b to the tetraacetate of conduramine E **15** (90%).<sup>8c,10</sup>









Applying the same one-flask reduction/acylation condition to the 1,2-type allylic azide **10a** cleanly effected the desired transformation to afford conduramine A-1 tetraacetate **16** (79%) (Scheme 4).<sup>11</sup> The azido carbonate **4**, a pivotal bridging intermediate en route to (+)-pancratistatin,<sup>12</sup> was also accessible from azide **10a**. Thus CF<sub>3</sub>COOH-catalyzed migration of the 2,3-*O*-isopropylidene group with relief of

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strain in the *trans* fused bicyclic system followed by in situ trapping of the azido alcohol with ClCOOMe/NaH resulted in efficient formation of the enantiopure carbonate **4** in 60% yield.

In summary, a new strategy invoking a new application of the [3,3] sigmatropic rearrangement of allylic azides and the presence of a  $C_2$  symmetry element within the pool of chiral substrates was evolved. Not only does this simple flexible strategy provide a concise approach to (+)-valienamine, but it also can readily be adopted for the synthesis of conduramine A-1, conduramine E, and the enantiopure azido carbonate **4**, a key intermediate of pancratistatin. This flexible technology provided above should be applicable to the construction of various structurally related natural products and other members of aminocyclitols. In addition, this study opens the question of the importance of the 1,3-diaxial interactions on the equilibrations of the allylic azides.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support.

**Supporting Information Available:** Experimental procedures and characterization data for 4, 6–8, 10a, 10b, 11–13, 1-derived pentaacetate 14, 2-derived tetraacetate 15, and 3-derived tetraacetate 16. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9016194