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Stereodivergent total asymmetric synthesis of polyhydroxylated pyrrolidines via tandem allylic epoxidation and intramolecular cyclization reactions

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Abstract—Epoxidation of the allylic alcohols **10** and **11** using the $VO(acac)_2$/*t*-BuOOH system followed by an intramolecular 5-*exo* cyclization of the resulting δ-epoxycarbamates **12**, **13**, **18**, and **19** has been shown to provide a general and efficient solution for the asymmetric synthesis of polyhydroxy pyrrolidines. The requisite vicinal amino alcohol functionality was enantio-/regio-selectively installed by the Os-catalyzed asymmetric aminohydroxylation reaction of the designed achiral olefin **6**.

Pyrrolidines have been found in a large number of biologically active natural and artificial compounds.[1] Among them, a certain class of polyhydroxylated pyrrolidines such as shown in Figure 1 has drawn considerable interest in recent years, primarily due to their ability to inhibit glycosidases.[2] Considering the implication of glycosidases in many serious diseases like diabetes,[3] cancers,[4] and viral infections including HIV,[5] such compounds and their derivatives may find useful therapeutic applications for treating these medical conditions. Furthermore, chiral polyhydroxylated pyrrolidines have been used as catalysts/ligands in asymmetric synthesis.[6] As a result, a range of strategies for the asymmetric synthesis of polyhydroxylated pyrrolidines have been developed, most of which have relied on use of chirons derived from carbohydrates, tartaric acid, pyrroles, and α-amino acids.[7] Recently, we developed the first true asymmetric methodology for the synthesis of polyhydroxylated pyrrolidines, which used the readily available olefin **6** as a starting material, and utilized the regioselective asymmetric aminohydroxylation (RAA) and amidomercuration reactions for installing the vicinal amino alcohol functionality and five-membered ring, respectively.[8] Herein, we now report that the RAA reaction as well as the epoxidation–intramolecular cyclization cascade of allylic alcohols can provide a more general and efficient solution for the complete asymmetric synthesis of polyhydroxylated pyrrolidines.

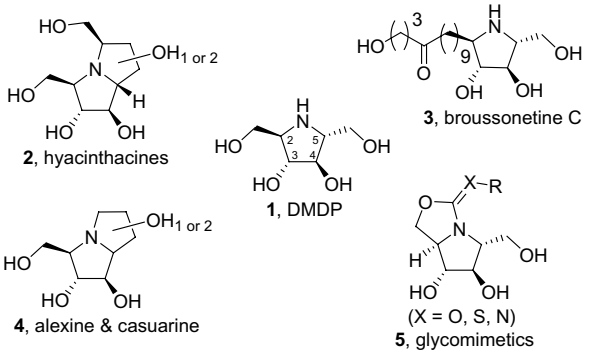

Figure 1.

From a synthetic point of view, it would not be unreasonable to think that **2**–**5** are the more complex derivatives of **1**, and thus can be synthesized by elaborating **1**. Therefore, any general and unified methodology for the asymmetric synthesis of these compounds should involve the asymmetric synthesis of **1** and its stereoisomers. Figure 2 describes a retrosynthetic analysis for the asymmetric synthesis of polyhydroxylated pyrrolidines including **1**. In this strategy, the RAA reaction (**V** to **IV**) and allylic epoxidation–cyclization reactions (**III**

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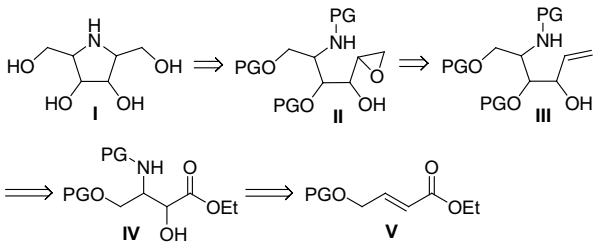
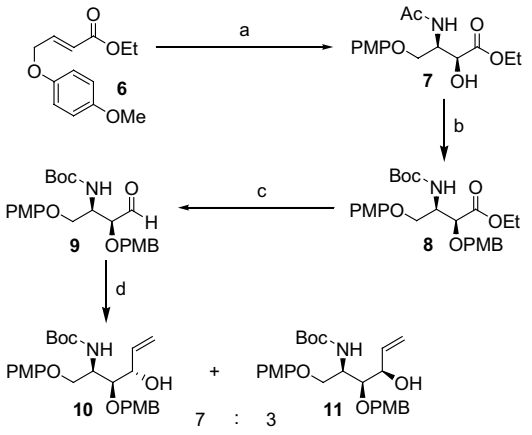


Figure 2. A retrosynthetic route to polyhydroxylated pyrrolidines.

to **I** through **II**) are used to establish two key structural features of polyhydroxylated pyrrolidines, the vicinal amino alcohol functionality and five-membered ring containing a nitrogen atom, respectively. Enantio- and regio-selective transformation of **V** to **IV** has been well established,[8] and a variety of reagents and catalysts are available for the stereoselective epoxidation of allylic alcohols.[9] In the allylic epoxidation reaction, it was hoped that the initially formed epoxide with right stereochemistry would spontaneously undergo an 5-*exo* intramolecular cyclization to give the corresponding pyrrolidine compound (direct conversion of **III** to **I**), making it easy to separate the other epoxide (if any) and the pyrrolidine compound.[10]

Scheme 1 delineates the synthesis of the optically pure substrates **10** and **11** required for the allylic epoxidation step. The RAA reaction of the olefin **6** using $(DHQD)_2PHAL$ and *N*-bromoacetamide afforded the *syn*-aminoalcohol **7** with an excellent regio- (>20:1) and enantio-selectivity (>99%). After protection of the hydroxyl group of **7** with *p*-methoxybenzyl (PMB) chloride and sodium hydride, the *N*-acetyl group of the resulting ester was transformed into *tert*-butyl carbamate (Boc) group employing di-*tert*-butyl carbonate in the presence of catalytic DMAP followed by a hydrazinolysis to provide **8**.[11] The partial reduction of the ester **8** with DIBAL at −78 °C afforded the aldehyde **9**, which upon

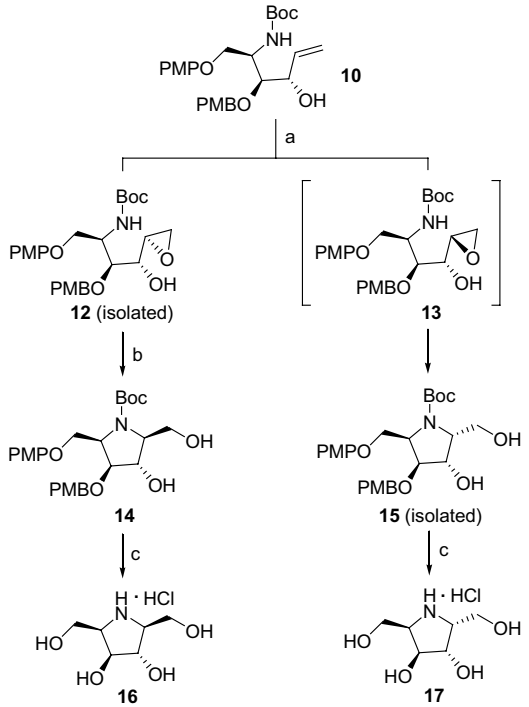


Scheme 1. Reagents and conditions: (a) $K_2OsO_4{\cdot}2H_2O$ (5 mol%), $(DHQD)_2PHAL$ (6 mol%), LiOH, *N*-bromoacetamide, *t*-BuOH–H_2O 2:1, 4 °C, 8 h, 70%; (b) (i) NaH, PMBCl, DMF, 0 °C, 10 h, 78%, (ii) $(Boc)_2O$, DMAP, THF, reflux, 4 h, then H_2NNH_2, MeOH, 4 h, 82%; (c) DIBAL, CH_2Cl_2, −78 °C, 3 h, 90%; (d) vinylmagnesium bromide, THF, −50 °C, 1 h, then room temp. 1 h, 88%.

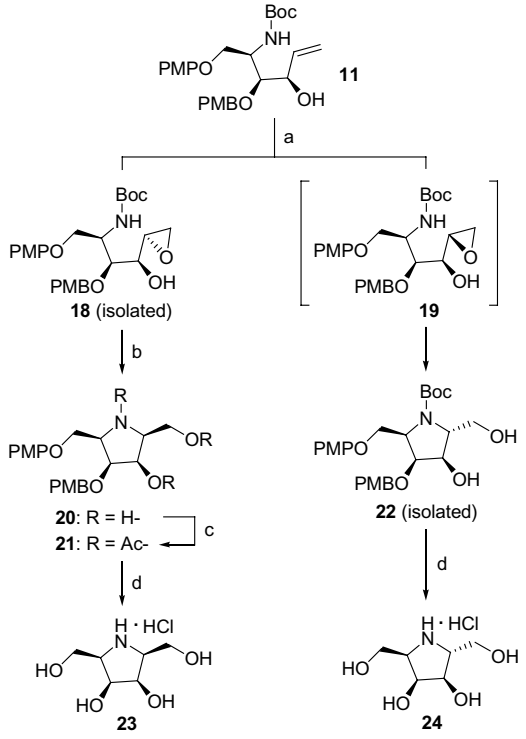
reaction with vinylmagnesium bromide at −50 °C generated the requisite allylic alcohols **10** and **11** in a 7:3 diastereoselectivity.

With the stage now set for the allylic epoxidation, **10** was treated with various epoxidation reagents including peracetic acid, MCPBA, $VO(acac)_2$/ROOH, and Sharpless asymmetric epoxidation reagents, among which the $VO(acac)_2$/*t*-BuOOH(TBHP) system gave the best results. After some experiments with $VO(acac)_2$/*t*-BuOOH/solvents, it was found that the reaction conditions using two-fold excess of TBHP in the presence of 4 mol% of $VO(acac)_2$ in toluene solvent at ambient temperature were optimal for the epoxidation of **10**.[12] Thus, under these conditions, **10** was smoothly transformed to a mixture of the epoxide **12** and the pyrrolidine **15** in 40% and 44% isolated yield, respectively (Scheme 2). The compound **15** is formed by the ring opening and concomitant intramolecular cyclization reactions of the initially formed epoxide **13** under the reaction conditions. After separation, cyclization of the surviving epoxide **12** in the presence of TFA (1.0 equiv) at 4 °C afforded the other diastereomeric pyrrolidine **14**. Deprotection of the PMP group of **14** and **15** by CAN[13] followed by exhaustive acidic hydrolysis of the resulting triols furnished the polyhydroxylated pyrrolidine **16** and **17** as their HCl salt, respectively.[14]

Epoxidation of the allylic alcohol **11** under the similar conditions was substantially slower compared to that of **10**, and thus most of the starting material remained even after 3 days. However, upon increasing temperature to



Scheme 2. Reagents and conditions: (a) $VO(acac)_2$ (4 mol%), TBHP (2.0 equiv), toluene, rt, 16 h, 40% for **12** and 44% for **15**; (b) TFA (1.0 equiv), CH_2Cl_2, 4 °C, 3 h, 82%; (c) (i) CAN, CH_3CN–H_2O 4:1, 4 °C, 10 min, (ii) 3 N HCl, 3 h, 76% for two steps.



Scheme 3. Reagents and conditions: (a) $VO(acac)_2$ (4 mol %), TBHP (2.0 equiv), toluene, 60 °C, 32 h, 38% for **18** and 42% for **22**; (b) TFA (2.5 equiv), CH_2Cl_2, rt, 32 h; (c) Ac_2O, Et_3N, CH_2Cl_2, 82%; (d) (i) CAN, CH_3CN–H_2O 4:1, 4 °C, 10 min, (ii) 3 N HCl, 3 h, 76% for two steps.

60 °C, the reaction completed in 32 h giving a mixture of the epoxide **18** and cyclized product **22** in 38% and 42% isolated yield, respectively (Scheme 3). Cyclization of the epoxide **18** needed more demanding conditions, where 2.5 equiv of TFA and ambient temperature were required. As a result, deprotection of the *N*-Boc group occurred to give the cyclic amine **20**. Even though ion-exchange column chromatography could be used for purification, the amine **20** was more conveniently purified by silica gel column chromatography after conversion to the corresponding tri-acetate **21**. Finally, upon successive CAN deprotection and acidic hydrolysis, **21** and **22** generated the polyhydroxylated pyrrolidines **23** and **24** as HCl salt, respectively.[15]

In summary, it has been shown that the RAA reaction of olefins and the epoxidation–intramolecular cyclization cascade of allylic alcohols can provide an extremely convenient tool for the asymmetric synthesis of polyhydroxylated pyrrolidines. Coupled with the previous work from this laboratory where the RAA reaction of olefins and oxazoline chemistry have been used to control stereochemistry of the vicinal amino alcohol functionality (stereochemistry at C-1 and C-2; see Fig. 1 for carbon numbering),[8c] the methodology reported here should make it possible to stereoselectively synthesize DMDP (**1**) and its all other stereoisomers from the readily available achiral olefin **6**. As an extension and application of the present methodology, the asymmetric synthesis of **2**, **3**, **4**, and **5** in Figure 1 are currently being pursued, and will be reported in due course.

Acknowledgements

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11. (a) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054; (b) To prepare the *N*-Boc protected **6** directly from **1**: the AA reaction of **1** with *N*-chloro-*tert*-butyl carbamate was attempted. However, the reaction suffered from a poor reaction yield, and further the desired product and *tert*-butyl carbamate could not be separated by column.
12. General procedure for vanadium-catalyzed epoxidation: To a stirred solution of **10** (1.19 g, 2.5 mmol) in anhydrous toluene (30 mL) was added $VO(acac)_2$ (27 mg, 0.1 mmol) and the atmosphere was replaced with a nitrogen stream. After 5 min TBHP (0.89 mL of 5.5 M decane solution, 5.0 mmol) was added dropwise. The resulting solution was stirred at rt for 16 h or until the starting material was completely consumed. The reaction mixture was poured in water (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×20 mL). The combined organic extracts were dried over Na_2SO_4, and the resulting solution was concentrated after filtration through a pad of Celite. The crude reaction mixture was purified by column chromatography (ethyl acetate–hexane 1:3) to give **12** and **15** as colorless oil. Compound **12**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H, *t*-Bu), 2.61–2.83 (m, 2H), 3.06 (dd, 1H $J = 4.4$ and 7.3 Hz), 3.60 (br s, 1H), 3.74 (s, 6H, $2\times CH_3$), 3.90–3.94 (distorted m, 2H), 4.19 (bs, 1H), 4.43–4.61 (m, 2H), 4.7 (d, 1H, $J = 10.7$ Hz), 4.98 (d, 1H, $J = 9.3$ Hz), 6.77–6.81 (m, 6H, ArH), 7.21 (d, 2H, $J = 8.3$ Hz). Compound **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (s, 9H, *t*-Bu), 3.74 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.79–3.81 (m, 2H), 3.84–3.89 (m, 1H), 3.92–4.15 (m, 2H), 4.16–4.21 (m, 3H), 4.58–4.62 (m, 2H), 6.76–6.82 (m, 6H), 7.21 (d, 2H, $J = 8.3$ Hz). Compound **18**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H, *t*-Bu), 2.69–2.70 (m, 1H), 2.85–2.87 (distorted dd, 1H), 3.18–3.21 (distorted dd, 1H), 3.77 (s, 7H, $2\times CH_3$ and CH), 3.82–3.88 (m, 2H), 3.95–3.98 (distorted dd, 1H), 4.37–4.44 (m, 1H), 4.50 (d, 1H, $J = 11.2$ Hz), 4.62 (dd, 1H, $J = 10.7$ and 13.7 Hz), 5.01 (d, 1H, $J = 9.8$ Hz), 6.80–6.83 (m, 6H, ArH), 7.21 (d, 2H, $J = 8.3$ Hz). Compound **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H, *t*-Bu), 3.76 (s, 4H, CH_3 and CH), 3.80 (s, 3H, CH_3), 3.86–3.90 (m, 2H), 4.40–4.16 (m, 4H), 4.38–4.40 (m, 1H), 4.52–4.57 (m, 1H), 4.68 (d, 1H, $J = 11.2$ Hz), 6.80–6.87 (m, 6H), 7.23 (d, 2H, $J = 8.3$ Hz).
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15. The spectral data of **23** are consistent with those reported in Wang, Y.-F.; Takaoka, Y.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1994**; *33*, 1242, and those of **24** agree well with those of its enantiomer reported in Cubero, I. I.; Lopez-Espiposa, M. T. P.; Diaz, R. R.; Montalban, F. F. *Carbohydr. Res.* **2001**; *330*, 401. Compound **23**: ^{1}H NMR (500 MHz, D_2O) δ 3.76–3.81 (m, 2H), 3.92 (dd, 2H, $J = 8.8$ and 12.2 Hz), 4.01 (dd, 2H, $J = 4.9$ and 12.2 Hz), 4.51 (d, $J = 4.9$ Hz); ^{13}C NMR (125 MHz, D_2O) δ 60.66, 64.30, 72.86. Compound **24**: ^{1}H NMR (500 MHz, D_2O) δ 3.64–3.68 (m, 2H), 3.78–3.82 (m, 4H), 3.86 (dd, 1H, $J = 4.9$ and 11.7 Hz), 3.98–4.02 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 56.49, 62.88, 65.47, 70.30, 74.67, 75.70.