Hg(II) Reagent-Controlled Stereoselective Synthesis of 2,5-*cis*- and 2,5-*trans*-Polyhydroxylated Pyrrolidines

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Abstract: Stereoselectivity in the intramolecular amidomercuration reaction of **11**, which could form 2,5-*cis*- and 2,5-*trans*-polyhydroxylated pyrrolidines, was found to be dependent on the nature of the Hg(II) salts used as well as on the stereochemistry and protection state of the hydroxyl group at the allylic carbon. Thus, the amidomercuration reaction of **11** with $Hg(CF_3CO_2)_2$ led to the predominant formation of the 2,5-*cis*-polyhydroxylated pyrrolidine **16**, while use of $Hg(CF_3SO_3)_2$ generated the corresponding 2,5-*trans* isomer **17**. Isomers **16** and **17** were further elaborated to stereoselectively synthesize 2,5-dideoxy 2,5-imino-D-altritol and 2,5-dideoxy 2,5-imino-D-galactitol (for **20** and **21**), which are known to be potent D-galactosidase inhibitors.

Key words: carbohydrate, glycosidase inhibitor, polyhydroxylated pyrrolidine, regioselective asymmetric aminohydroxylation reaction, intramolecular amidomercuration reaction

Naturally occurring polyhydroxylated pyrrolidines and pyrrolizidines such as (2*R*,3*R*,4*R*,5*R*)-bis(hydroxymethyl)dihydroxypyrrolidine (**1**: DMDP), hyacinthacines (**2** and **3**), australine (**4**), alexine (**5**), and casuarine (**6**) have displayed potent glycosidase inhibitory activities, and have also been shown to have some potential as antiviral and antiretroviral agents (Figure 1).[1] In addition to such profound biological activities, their intriguing structures have made them a subject of intense synthetic scrutiny in recent years.[2]

A plausible general strategy for the asymmetric total synthesis of these compounds would involve the asymmetric synthesis and further elaboration of DMDP and its stereoisomers. It was thought that, in connection with the previous works from this laboratory on the regioselective asymmetric aminohydroxylation reaction (RAA) of olefins,[3] intramolecular amidomercuration reaction of δ-alkenylcarbamates followed by oxidative demercuration reaction could provide a general and efficient route to these compounds (Scheme 1). Even though the intramolecular amidomercuration reaction has long been used for the construction of substituted pyrrolidine rings,[4] little research work has been done to the application of this reaction on a system like **II**, that could give rise to the direct asymmetric formation of polyhydroxylated pyrrolidine rings (**II** to **III** in Scheme 1).[5]

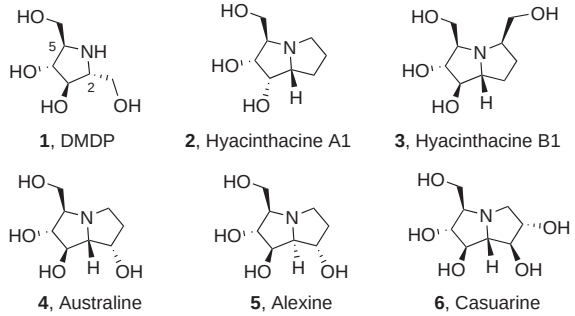
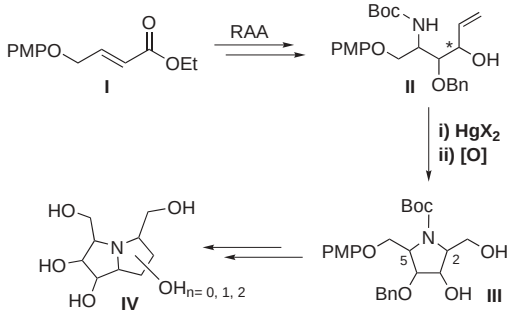


Figure 1 Potent polyhydroxylated pyrrolidine and pyrrolizidine inhibitors of glycosidases.



Scheme 1 A unified strategy for the asymmetric synthesis of polyhydroxylated pyrrolidines and pyrrolidizines.

Furthermore, since all intramolecular amidomercuration reactions of δ-alkenylcarbamates/amides reported up to date led to the predominant formation of *trans*-2,5-substituted pyrrolidine rings, developing a Hg(II)-mediated methodology for the stereoselective formation of *cis*-2,5-substituted pyrrolidine rings would greatly expand the synthetic scope of the intramolecular amidomercuration reactions. Herein, we demonstrate that the stereochemical outcome of the intramolecular amidomercuration reactions of **II** is dependent upon several factors such as the stereochemistry and protection state of the hydroxyl group at the allylic carbon (the carbon with an asterisk in Scheme 1) as well as the nature of the counterion in the mercury(II) salt used. Also reported is the complete stereoselective synthesis of two potent D-galactosidase inhibitors, namely 2,5-dideoxy 2,5-imino-D-galactitol and 2,5-dideoxy 2,5-imino-D-altritol via the methodology developed here.

The requisite δ-alkenylcarbamates **10**–**13** were prepared starting from the readily available α,β-unsaturated ester **I**[6] (Scheme 2). The RAA reaction of **I** using the

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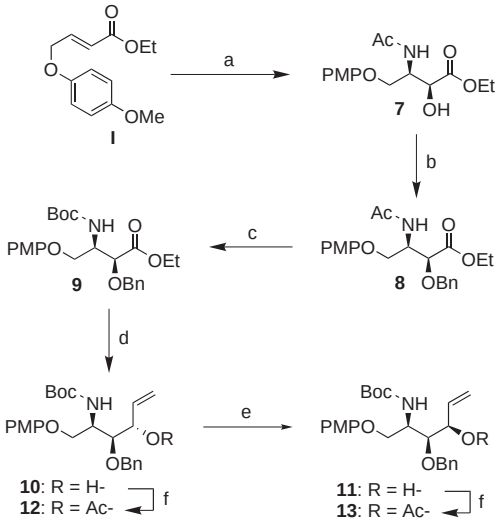
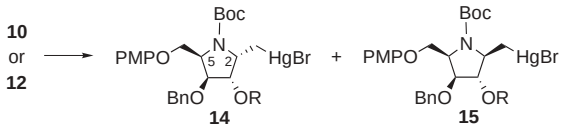


Scheme 2 Asymmetric synthesis of the substrates **10**–**13** for the intramolecular amidomercuration reactions. *Reagents and conditions*: (a) $K_2OsO_4{\cdot}2H_2O$ (5 mol%), $(DHQD)_2PHAL$ (6 mol%), LiOH, *N*-bromoacetamide, *t*-BuOH–H_2O 2:1, 4 °C, 8 h, 70%; (b) NaH, BnCl, DMF, 0 °C, 10 h, 78%; (c) (i) $(Boc)_2O$, DMAP, THF, reflux, 4 h; (ii) H_2NNH_2, MeOH, 4 h, 85%; (d) (i) DIBAL, CH_2Cl_2, –78 °C, 3 h, 90%; (ii) vinylmagnesium bromide, THF, –50 °C, 1 h then r.t. 1 h, 60%; (e) (i) PPh_3, DIAD, *p*-nitrobenzoic acid, THF; (ii) K_2CO_3, MeOH, 55%; (f) Ac_2O, DMAP (cat.), Et_3N, CH_2Cl_2, quantitative for **12** and **13**.

$(DHQD)_2PHAL$ as a ligand and *N*-bromoacetamide as a nitrogen source/oxidant afforded the *syn*-aminoalcohol **7** with an excellent regio-(>20:1) and enantioselectivity (>99% ee and 70% yield after one recrystallization from ethyl acetate). Protection of the hydroxyl group with benzylchloride and sodium hydride in DMF gave the benzyl ether **8**.[7] The *N*-acetyl group of **8** was converted to the *N*-Boc group to give the carbamate **9** by reacting with di-*tert*-butyl dicarbonate in the presence of catalytic DMAP followed by the cleavage of the *N*-acetyl group through hydrazinolysis.[8] Partial reduction of the ester **9** by slow addition of DIBAL at –78 °C and subsequent reaction of the resulting aldehyde with vinylmagnesium bromide generated the δ-alkenylcarbamate **10** in a 4:1 *S*:*R* diastereoselectivity. Stereochemistry of the hydroxy group in **10** was inverted by Mitsunobu reaction employing triphenylphosphine and diisopropyl azadicarboxylate in the presence of *p*-nitrobenzoic acid.[9] Transesterification of the resulting benzoate furnished the diastereomeric δ-alkenylcarbamate **11**. The alcohols **10** and **11** were converted into the corresponding acetates **12** and **13** by treatment with acetic anhydride, triethylamine, and a catalytic amount of DMAP. Compounds **10**–**13** were used to study the effects of stereochemistry and protection state of the allylic hydroxyl group on the stereoselectivity of their intramolecular amidomercuration reactions.

In general, regardless of the nature of the Hg(II) reagent and of the reaction temperature, the intramolecular amidomercuration reactions of **10** proceeded with predominant 2,5-*trans* selectivity in accordance with the previous observations (Table 1).[4,5] Protection of the allylic alcohol as the corresponding acetate did not change the stereochemical outcome (Table 1, entry 1 vs. 3 as well as entry 4 vs. 6). Relatively less reactive Hg(II) reagents such as methansulfonate, acetate, and fluoride salts required ambient temperature for the amidomercuration reactions (entries 7–12). When mercuric triflate was used, two equivalents of potassium carbonate were also needed to prevent deprotection of the Boc-group (entries 1–3).

Table 1 Amidomercuration Reactions of **10** and **12**

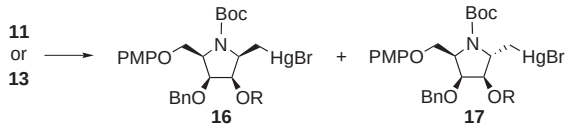


Entry	R	Reaction conditions[a]		Yield (%)	**14**:**15**
1	-H	$Hg(CF_3SO_3)_2$	A[b]	65	>15:1
2	-H		B[b]	60	>15:1
3	-Ac		A[b]	78	>15:1
4	-H	$Hg(CF_3CO_2)_2$	A	92	>15:1
5	-H		B	86	>15:1
6	-Ac		A	75	>15:1
7	-H	$Hg(CH_3SO_3)_2$	A	NR[c]	NR[c]
8	-H		B	79	>15:1
9	-H	$Hg(CH_3CO_2)_2$	A	NR[c]	NR[c]
10	-H		B	82	>15:1
11	-H	HgF_2	A	NR[c]	NR[c]
12	-H		B	90[d]	>15:1

[a] Condition A: –78 °C in THF then $NaHCO_3$, KBr. Condition B: at ambient temperature in THF then $NaHCO_3$, KBr.
[b] Two equivalents of K_2CO_3 were added to prevent the Boc-deprotection.
[c] NR: no reaction.
[d] Isolated as mercuric fluoride.

Given the present data as well as the previous literature results, it was anticipated that the intramolecular amidomercuration reaction of **11** and **13** should also occur with predominant 2,5-*trans* selectivity. To gain further insight into this possibility, the intramolecular amidomercuration reaction of the δ-alkenylcarbamates **11** and **13** was assessed under similar conditions (Table 2). Interestingly, in this case the reaction was found to be largely dependent on the nature of Hg(II) reagent, temperature, and/or protection state of the allylic alcohol functionality. Thus, mercuric triflate, mercuric acetate, and mercuric fluoride showed 2,5-*trans* selectivity, whereas mercuric trifluoroacetate, and mercuric methansulfonate exhibited 2,5-*cis* selectivity. Treatment of **11** with mercuric triflate at –78 °C followed by the addition of potassium bromide to the reaction mixture led to a mixture of the 2,5-*cis*- and 2,5-*trans*-pyrrolidines **16** and **17** in 1:6 ratio (entry 1).

Table 2 Amidomercuration Reactions of **11** and **13**

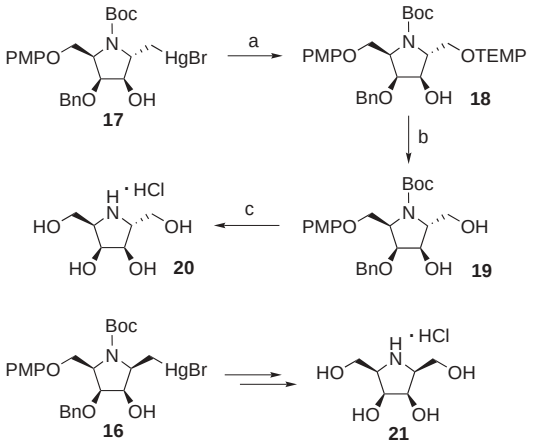


Entry	R	Reaction conditions[a]		Yield (%)	**16**:**17**
1	-H	**$Hg(CF_3SO_3)_2$**	**A**[b]	**95**	**1:6**
2	-H		**B**[b]	**87**	**1:6**
3	-Ac		A[b]	73	2:3
4	-H	**$Hg(CF_3CO_2)_2$**	**A**	**82**	**15:1**
5	-H		B	85	3:1
6	-Ac		A	69	3:2
7	-H	$Hg(CH_3SO_3)_2$	A	NR[c]	NR[c]
8	-H		B	83	2:1
9	-H	$Hg(CH_3CO_2)_2$	A	NR[c]	NR[c]
10	-H		B	79	1:2
11	-H	HgF_2	A	NR[c]	NR[c]
12	-H		B[d]	93[d]	1:3

[a] Condition A: –78 °C in THF then $NaHCO_3$, KBr. Condition B: at ambient temperature in THF then $NaHCO_3$, KBr.
[b] Two equivalents of K_2CO_3 were added to prevent the Boc-deprotection.
[c] NR: no reaction.
[d] Isolated as mercuric fluoride.

Similar results were obtained at ambient temperature (entry 2). However, to our pleasant surprise, reaction of **11** with mercuric trifluoroacetate at –78 °C generated the 2,5-*cis*-pyrrolidine **16** with a high selectivity (15:1, entry 4). The selectivity decreased to 3:1 at room temperature (entry 5). To the best of our knowledge, 2,5-*cis* selectivity has not been previously observed in the intramolecular amidomercuration reaction of δ-alkenylcarbamates/amides. Regardless of the Hg(II) reagent used, protection of the hydroxyl group as its acetate resulted in a loss of selectivity (entries 3 and 6). As before, mercuric acetate, mercuric methanesulfonate, and mercuric fluoride failed to react at –78 °C (entries 7, 9 and 11), but at room temperature they led to pyrrolidine formation with low selectivities (entries 8, 10 and 12). Although the exact cause for the stereodivergence in the intramolecular amidomercuration reaction of **11** and **13** remains to be investigated further, the present results indicate that steric factor and directing effect by the allylic hydroxyl group are interplaying. Nonetheless, it is shown that a judicious selection of the Hg(II) reagent and reaction temperature in the intramolecular amidomercuration reaction of **11** enables the stereoselective formation of 2,5-*cis*- and 2,5-*trans*-polyhydroxylated pyrolidines, **16** and **17**.

Finally, the developed methodology was applied to the stereoselective synthesis of 2,5-dideoxy-2,5-imino-D-altritol (**20**) and 2,5-dideoxy-2,5-imino-D-galactitol (**21**), which were known to be potent D-galactosidase inhibitors (Scheme 3).[10] Oxidative–demercuration reaction of **17** with $NaBH_4$–TEMPO–O_2 furnished the TEMPO adduct **18**,[11] which was converted to the diol **19** by treatment of Zn/HOAc. Deprotection of PMP, Boc, and benzyl groups by CAN,[12] 3 N HCl, and hydrogenation, respectively, converted **19** to **20**. Similarly, **21** was obtained from **16**. The spectral data (^{1}H NMR and ^{13}C NMR) of **20** and **21** were found to be consistent with those reported in the literature.[10b,13]



Scheme 3 Stereoselective synthesis of the potent galactosidase inhibitors **20** and **21**. *Reagents and conditions:* (a) O_2, TEMPO (10 equiv), $NaBH_4$, DMF, 15 min, 75%; (b) Zn, HOAc–THF–H_20 3:1:1, 80 °C, 1 h, 85%; (c) (i) CAN, MeCN–H_2O 4:1, 4 °C, 10 min; (ii) 3 N HCl, EtOAc, 30 min; (iii) Pd/C, H_2, 24 h, 78% for three steps.

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(13) **Compound 14**: $[\alpha]_D$ +20.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (5 H, m), 6.82–6.75 (4 H, m), 4.77–4.64 (1 H, m), 4.60–4.55 (2 H, m), 4.25 and 3.84 (1 H, br s), 4.20–4.02 (5 H, m), 3.75 (3 H, s), 2.30 and 2.11 (1 H, m,) 1.59 and 1.30 (1 H, t, *J* = 10.5 Hz), 1.44 and 1.40 (9 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.0, 153.9, 152.8, 137.4, 128.6, 128.2, 127.8, 115.9, 114.6, 81.3, 80.9, 73.4, 71.6, 65.4, 56.7, 55.6, 55.3, 30.3, 28.4, minor peaks due to rotational isomer(s): 81.0, 80.4, 73.7, 71.6, 70.8, 65.4, 64.1, 58.9, 54.6. **Compound 16**: $[\alpha]_D$ +50.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.28 (5 H, m), 6.93 (2 H, d, *J* = 9.0 Hz), 6.83 (2 H, d, *J* = 9.0 Hz), 4.71 (1 H, d, *J* = 11.5 Hz), 4.67 (1 H, d, *J* = 11.5 Hz), 4.25–4.12 (6 H, m), 3.78–3.70 (1 H, m), 3.77 (3 H, s), 2.25 (1 H, dd, *J* = 11.5 and 6.0 Hz), 2.17 (1 H, dd, *J* = 11.5 and 4.5 Hz), 1.48 (9 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.1, 154.5, 151.9, 137.3, 128.5, 128.1, 127.9, 116.2, 114.7, 81.2, 77.1, 72.6, 70.9, 66.7, 60.1, 59.1, 55.7, 34.0, 28.5. **Compound 17**: $[\alpha]_D$ +19.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.20 (5 H, m), 6.85–6.70 (4 H, m), 4.72 (1 H, d, *J* = 11.5 Hz), 4.51 (1 H, d, *J* = 11.5 Hz), 4.50–4.35 (2 H, m), 4.25–4.10 (3 H, m), 4.00 (1 H, br s), 3.71 (3 H, s), 1.91 (1 H, d, *J* = 12.0 Hz), 1.48 (1 H, d, *J* = 12.0 Hz), 1.32 (9 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 154.1, 152.0, 137.3, 128.5, 128.0, 127.7, 116.8, 114.6, 81.6, 75.9, 75.8, 71.4, 65.5, 65.4, 58.3, 55.6, 35.0, 28.4.