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Regioselective asymmetric aminohydroxylation of precursors to 2,3,6-trideoxy-3-aminohexoses

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Abstract

The catalytic asymmetric aminohydroxylation (AA) of 5-substituted-pent-2-enoates **8** and **17** was investigated as a route to 2,3,6-trideoxy-3-aminohexoses. The AA of ester **8**, which bears a dimethyl acetal at C-5, favoured formation of the α-amino regioisomer **11** with optimum regioselectivity being observed using $(DHQ)_2AQN$ as the chiral ligand and the chloramine salt of ethyl carbamate as the nitrogen source. Ester **17**, which has a 4-methoxyphenoxy group at C-5, undergoes highly regioselective AA affording the β-amino regioisomer **19** in excellent enantiomeric excess, thereby establishing that introduction of this aromatic group leads to a superior substrate for AA. © 2000 Elsevier Science Ltd. All rights reserved.

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The Sharpless asymmetric aminohydroxylation (AA) provides a one-step preparation of protected β-amino alcohols from alkenes using osmium tetroxide and cinchona alkaloid-derived chiral ligands.[1] Several procedures have been developed[2] to improve the scope and selectivity of this reaction which include the use of sulfonamides,[1a,3] amides,[4] carbamates[5] and aminoheterocycles[6] as the nitrogen source/oxidant. The AA transformation has been used as the pivotal step in the synthesis of many biologically important molecules, e.g. amino cyclitols,[7] the Taxol™ side chain,[8] β-amino-α-hydroxyphosphonic acid derivatives[9] and α-amino acids.[5d,10]

As part of our synthetic studies towards the *C*-glycoside containing pyranonaphthoquinone antibiotic medermycin (**1**),[11] we required an efficient synthesis of the amino-sugar component, D-angolosamine (**2**, 3-dimethylamino-2,3,6-trideoxy-D-arabino-hexopyranose). Traditional synthetic approaches[12] to 3-amino sugars have relied on lengthy enantiospecific syntheses based on readily available D- and L-carbohydrates as starting materials. The asymmetric synthesis of these sugars from non-carbohydrate sources has been studied[12,13] with a Sharpless asymmetric epoxidation/

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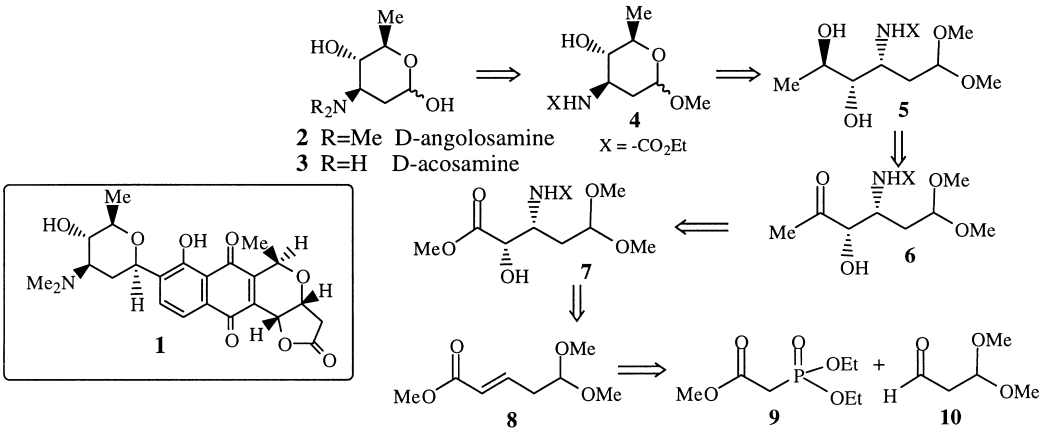
kinetic resolution strategy[14] providing a notably efficient synthesis of the requisite 2,3,6-trideoxy-3-aminohexoses. Given that control of the amino alcohol functionality at C-3 and C-4 of these sugars is a crucial factor in the development of a new synthesis, we decided to embark on a catalytic asymmetric synthesis of D-angolosamine **2** in which AA of an acyclic precursor was a pivotal step. This approach is also amenable to the synthesis of both naturally occurring D- and L-forms of the parent amino sugar acosamine **3**. To date the asymmetric synthesis of 3-amino sugars using the powerful AA reaction to install the requisite 3-amino-4-hydroxy group has not been realised and is the subject of the work reported herein.

D-Angolosamine **2** is derived from carbamate **4** which in turn is derived from acyclic dimethyl acetal **5**, itself available via chelation-controlled reduction of ketone **6** (Scheme 1). Given that α,β-unsaturated esters have proven to be excellent substrates for the AA reaction, methyl ester **7** provides a suitable precursor for ketone **6**, which is then available via the crucial AA of α,β-unsaturated ester **8**. Key to the success of this strategy is the effective control of the regioselectivity of the AA reaction. Ester **8**[15] was readily prepared in 84% yield via Wadsworth–Emmons olefination of aldehyde **10**[16] with phosphonate **9** using sodium hydride in benzene.

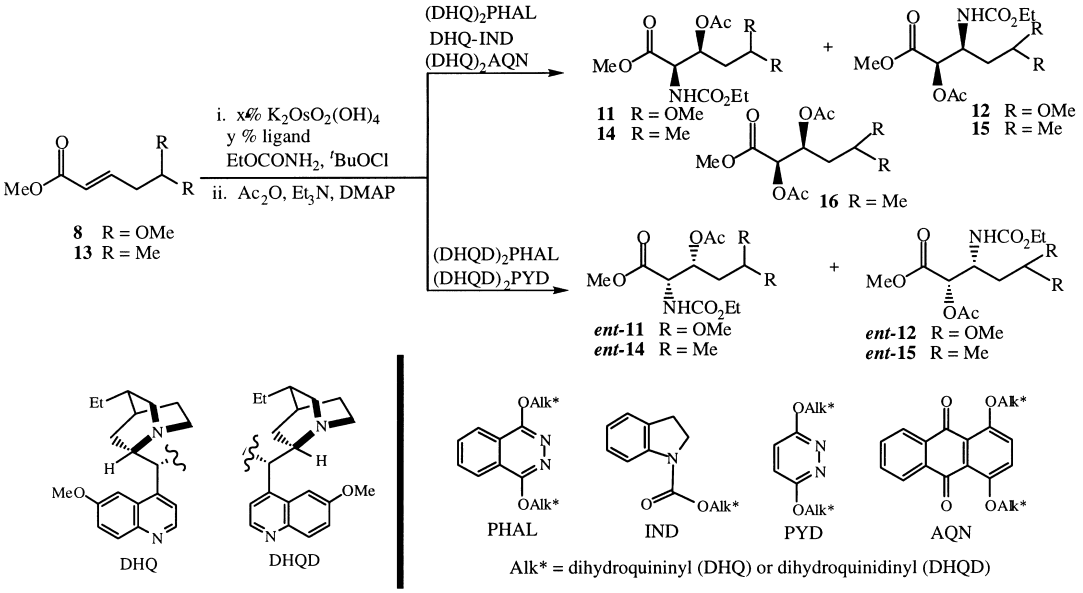


Scheme 1.

The AA of ester **8** was performed using ethyl carbamate as the nitrogen source and an increased catalyst loading of 8% to facilitate complete conversion (Table 1). The crude reaction mixture was acetylated in order to allow separation of the regioisomeric products **11** and **12**. In order to study the effects of the chiral ligand on the AA of ester **8**, reactions were performed using DHQ-IND, $(DHQD)_2PYD$ and $(DHQ)_2AQN$ (Table 1, entries 3–5). All three ligands resulted in improved regioselectivity for the undesired α-amino isomer **11** compared to the use of $(DHQ)_2PHAL$. The most dramatic effect was observed using $(DHQ)_2AQN$ which has been observed[4,17] to reverse the sense of regioselectivity for styrene and methyl cinnamate substrates, and resulted in a dramatic 11.0:1 selectivity for **11** over **12**.[18]

Production of the undesired regioisomer in the AA reaction led us to investigate the structural features of the substrate responsible for regiocontrol and enantioselectivity. When the dimethyl acetal in ester **8** was replaced by a sterically similar isopropyl group (ester **13**) the β-amino isomer **15** was favoured over the α-amino isomer **14** in the AA reaction using the standard ligands $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ (Table 1); however, the regioselectivity observed in both

Table 1
Asymmetric aminohydroxylation of esters **8** and **13**



Catalyst loading	Ligand	Substrate in 50% aq. ^{n}PrOH	Yield[a]	Regioselectivity[b]	e.e.(%)[c]	$[\alpha]_D$[d]
8%[e]	10% $(DHQ)_2PHAL$	**8**[f]	93%	1.3:1	**11** 78[g,h]	-35.1
				11:**12**	**12** 83[g,h]	-32.3
8%	10% (DHQD),PHAL	**8**	77%	1.5:1	***ent*-11** 67	+34.4
				***ent*-11**: ***ent*-12**	***ent*-12** 71	+30.8
8%	10% DHQ-IND	**8**	60%	3.4:1		
				11:**12**		
8%	10% (DHQD),PYD	**8**	49%	2.0:1		
				***ent*-11**: ***ent*-12**		
8%	10% $(DHQ)_2AQN$	**8**	57%	11.0:1	**11** 89	-38.2
				11:**12**		
4%	5% $(DHQ)_2PHAL$	**13**	41%	1:2.3	**14** 70	-36.0
			(+ 12% **16**)	**14**: **15**	**15** 60	-40.0
4%	5% (DHQD),PHAL	**13**	32%	1:1.3	***ent*-14** 76[g]	+36.3
			(+ 5% **16**)	***ent*-14**: ***ent*-15**	***ent*-15** 83[g]	+45.4

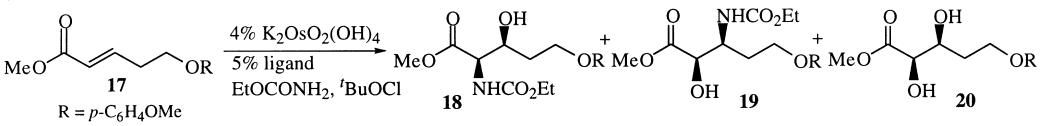
[a] Combined yield of **11** and **12** or **14** and **15** prior to separation. [b] Ratio determined by ^1H NMR (200 MHz) integration [c] Determined by deacetylation and conversion to *R*- and/or *S*-α-methoxy-α-(trifluoromethyl)phenyl acetate derivatives. [d] Optical rotation recorded in dichloromethane solution (c 0.5 - 1.5). [e] Reaction with lower catalyst loadings, 4% and 6% gave combined yields of 34% and 65% respectively. [f] Reactions conducted in 50% aqueous ^{t}BuOH and CH_3CN gave combined yields of 45% (1.7:1 **11**:**12**) and 56% (1.3:1 **11**:**12**). [g] Absolute configuration determined by Mosher's method. [h] Enantiomeric excess determined by NMR analysis with (*R*)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Enantiomeric excess within +/-5% of that determined by Mosher's ester analysis.

cases was poor. Other important differences in the AA reaction of ester **13** compared to ester **8** were the lower catalyst loading (4%) and the substantial quantity of diacetate by-product **16** observed in the case of ester **13**.

The Criegee, Corey and NOE qualitative model[19] for the Sharpless asymmetric dihydroxylation (AD) reaction predicts that substrates with suitably positioned aromatic systems should give high enantioselectivity due to favourable π-stacking interactions between the substrate and the ligand. With this idea in mind, we focused on the AA reaction of *p*-methoxyphenyl substituted ester **17**

(Table 2). Gratifyingly, use of ester **17** provided high regioselectivity {13:1 using $(DHQD)_2PHAL$, 20:1 using $(DHQ)_2PHAL$} for the β-amino isomer **19** over the α-amino isomer **18**. The ee observed for this isomer, **19** was 98% and for **ent-19**, 89% supporting the hypothesis that AA of α,β-unsaturated esters proceeds more regioselectively in favour of the β-amino isomer when an aromatic ring can interact favourably with the chiral ligand in the kinetically favoured transition state. The AA of **17** extends the range of substrates known to undergo highly regio- and enantioselective AA reactions and adds to the rapidly growing body of knowledge on harnessing substrate control to influence the outcome of the AA reaction.[10,17,20]

Table 2
Asymmetric aminohydroxylation of ester **17**



Catalyst loading	Ligand	Solvent 50% aq.	Yield[a]	Regioselectivity[b]	e.e.(%)[c]	$[\alpha]_D$[d]
4%	5% $(DHQ)_2PHAL$	^{n}PrOH	59% (+ 21% **20**)	1:>20 **18**[e]:**19**	**19** 98[f]	-57.4°
4%	5% $(DHQD)_2PHAL$	^{n}PrOH	63% (+ 24% ***ent*-20**)	1:13 ***ent*-18**[e]:***ent*-19**	***ent*-19** 89	+48.9°

[a] Yield of **19**. [b] Ratio determined by ^{1}H NMR (200 MHz) integration of crude reaction mixture. [c] Determined by conversion to *R* and/or *S*-α-methoxy-α-(trifluoromethyl)phenyl acetate derivatives. [d] Optical rotation recorded in dichloromethane solution (c 0.5 1.5). [e] Not isolated. [f] Absolute configuration determined by Mosher's method.

In summary, incorporation of an aryloxy group at C-5 of ester **17** afforded an excellent substrate for highly enantioselective and regioselective AA, thereby providing a starting point for the asymmetric synthesis of 2,3,6-trideoxy-3-aminohexoses. Alternatively, use of $(DHQ)_2AQN$ in the AA of ester **8** afforded α-amino isomer **11** in excellent ee which will serve as a starting point for the asymmetric synthesis of D- and L-2,3,6-trideoxy-4-aminohexoses.

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