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DIASTEREOCONTROL IN THE ASYMMETRIC DIHYDROXYLATION OF CHIRAL 3-ALKENYL-4,5-DIHYDROISOXAZOLES

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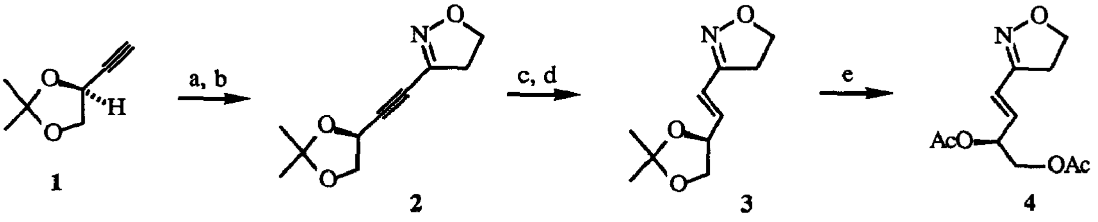
Summary: Catalytic asymmetric dihydroxylation of **4** afforded virtually one diastereomer using $(DHQD)_2$-PHAL as a chiral auxiliary (matched pair; 96% d.e.); the other diastereomer was heavily predominant with $(DHQ)_2$-PHAL as the chiral auxiliary (mismatched pair; 90% d.e.).

The 4,5-dihydroisoxazoles (DHI's) have been used as precursors to a number of aminosugars and related compounds.[1] Their synthetic utility would be significantly extended by the devlopment of efficient methods to dihydroxylate an alkenyl sidechain attached to the 3-position of the ring. In connection with this matter, we have prepared the optically active alkenyl DHI's **3** and **4** and subjected them to asymmetric dihydroxylation (AD) under a variety of conditions, especially those recently recommended by Sharpless *et al.*[2]

The starting material chosen for preparation of alkenyl DHI **3** was the known[3] optically active alkyne **1** (Scheme 1). The anion of **1** was prepared using excess *n*-butyllithium and was added to excess 3-nitro-4,5-dihydroisoxazole[4] at 0-5 °C. The resulting alkynyl DHI **2**[5] was obtained pure in 76% yield after chromatography and Kugelrohr distillation. Lindlar reduction of alkynyl DHI **2** followed by iodine catalyzed *cis* → *trans*

Scheme 1.

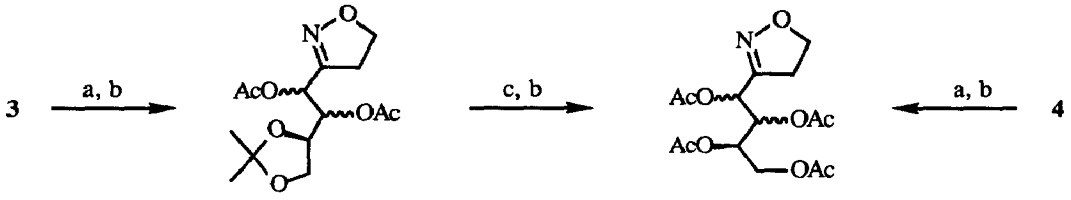


[a] 1.5 eq *n*-BuLi, THF, -78 °C. [b] 1.5 eq 3-nitro-4,5-dihydroisoxazole, 0-5 ° C. [c] 1 atm H_2, Lindlar cat, quinoline. [d] cat I_2, hν (sunlamp), PhH. [e] pyridinium tosylate, MeOH then Ac_2O, pyridine.

isomerization afforded alkenyl DHI **3** in 67% overall yield for the two steps. Removal of the acetonide using pyridinium tosylate[6] followed by acetylation afforded alkenyl DHI **4** in 94% yield from **3**.

The dihydroxylation of alkenyl DHI's **3** and **4** was first investigated using achiral reagents according to the osmium-catalyzed procedure developed by the Upjohn group[7] (Scheme 2). Alkenyl DHI **3** was converted to a mixture of diols which was directly acetylated. The resulting diacetates **5a** and **5b** were obtained with a 77:23 ratio in 85% yield (Table 1, entry 1). Based on Kishi's model[8], hydroxylation *anti* to the allylic *O*-substituent would be anticipated for **3** so that the major product should be **5a**. Similarly, tetraacetates **6a** and **6b** were obtained with a 76:24 ratio in 83% yield. Diacetates **5** (**5a**/**5b**, 88:12) were converted to tetraacetates **6** (**6a**/**6b**, 88:12) to determine which isomers had the same relative configuration.

Scheme 2.



5a, *anti*, AcO····
b, *syn*, AcO▬

6a, *anti*, AcO····
b, *syn*, AcO▬

[a] see Table 1. [b] excess Ac_2O, pyridine. [c] pyridinium tosylate, MeOH.

Using optically active alkenyl DHI's **3** and **4** as substrates for the AD reaction constitutes a double asymmetric synthesis. One can envision a matched pair and a mismatched pair of stereoisomers. The DHQD-MEQ[9] and $(DHQD)_2$-PHAL[2] chiral systems recommended by Sharpless *et al* would be expected to promote *anti*-addition: application of these chiral auxiliaries to **3** then should constitute the matched pair affording diacetate **5a** as the major product after acetylation. This proved correct although the degree of diastereoselectivity was disappointing for our initial results with the DHQD-MEQ system either under catalytic or stoichiometric conditions (Table 1, entries 3-4). However, the $(DHQD)_2$-PHAL system proved quite satisfactory under a slight, but essential, modification of the recommended[2] catalytic conditions. It was necessary to use 0.08 mole equivalents of potassium osmate for efficient dihydroxylation of **3**.[10] After acetylation of the crude diols, the diacetates **5a** and **5b** were obtained with a 96:4 ratio in 53% overall yield.

Kishi reported[8a-b] that allylic acetates are dihydroxylated by osmium tetroxide with poor diastereoselectivity in the absence of any chiral auxiliary. Application of the $(DHQD)_2$-PHAL catalytic system to the AD reaction of **4** again afforded a very promising result: acetylation of the initially formed diols afforded predominantly one tetraacetate (**6a**/**6b**, 98:2) in 82% yield.

While the preceding results might be expected for the matched pair of stereoisomers, at the outset of this work it was not at all clear what would occur with the mismatched pair.[11] The initial experiments with DHQ-MEQ were again discouraging in that dihydroxylation of **4** gave a 52:48 diastereomer ratio. However, application of the (DHQ)$_2$-PHAL system to **4** under catalytic conditions proved highly beneficial. After acetylation of the diols, the tetraacetates **6a** and **6b** were obtained with a 5:95 ratio in 85% overall yield. Thus, the chiral auxiliary in the AD reaction was able to control the stereochemical outcome despite the natural proclivity of the chiral substrate. Fair diastereoselectivity in the mismatched direction was also obtained for the alkenyl DHI **3**: the diacetates **5a** and **5b** were obtained with an 11:89 ratio in 62% overall yield. The intermediate diols could be separated by preparative chromatography so that pure **5a** and **5b** were obtained.

TABLE 1. DIHYDROXYLATION OF DHI's **3** AND **4**.

entry	substrate	chiral auxiliary	conditions	*anti* /*syn* [a]	yield, % [b]
1	**3**	none	cat achiral [c]	77 : 23	85
2	**4**	none	cat achiral [c]	76 : 24	83
3	**3**	DHQD-MEQ	cat chiral [c,d]	89 : 11	52
4	**3**	DHQD-MEQ	stoich chiral [e]	78 : 22	48
5	**4**	DHQ-MEQ	cat chiral [f]	52 : 48	66
6	**3**	(DHQD)$_2$-PHAL	cat chiral [f]	96 : 4	53
7	**3**	(DHQ)$_2$-PHAL	cat chiral [f,g]	11 : 89	62 [h]
8	**4**	(DHQD)$_2$-PHAL	cat chiral [f]	98 : 2	82
9	**4**	(DHQ)$_2$-PHAL	cat chiral [f]	5 : 95	85

[a] by HPLC on a Microsorb™ silica column (hexanes-*i*-PrOH, 90:10 [tetraacetates] or 95:5 [diacetates]). [b] isolated by prep TLC. [c] 0.1 eq OsO_4, 3 eq NMO, THF-water, 9:1, 20 °C. [d] 0.4 eq chiral aux. [e] 3 eq chiral aux, 1 eq OsO_4, toluene, 20 °C. [f] 0.08 eq $K_2OsO_4 \cdot 2H_2O$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 0.4 eq chiral aux, 1 eq $MeSO_2NH_2$, water-*t*-BuOH, 1:1, 20 °C. [g] use of AD-mix-α under the conditions recommended in reference 2 gave only 20% reaction after 22 h. [h] using either 0.08 eq or 0.4 eq chiral aux.

In conclusion, high diastereoselectivity was obtained for osmium-catalyzed dihydroxylation of alkenyl DHI **4** either *anti* or *syn* to the allylic acetate group. The resulting optically active DHI's are under investigation as intermediates for aminosugar synthesis.

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5. Representative ^{1}H-NMR spectra in $CDCl_3$: **2** δ 4.84 (apparent t, 1H), 4.39 (t, 2H, *J*=10.4 Hz), 4.17 (dd, 1H, *J*=6.5, 8.2 Hz), 3.96 (dd, 1H, *J*=6.0, 8.2 Hz), 3.02 (t, 2H, *J*=10.4 Hz), 1.45 (s, 3H), and 1.35 (s, 3H); **3** δ 6.70 (d, 1H, *J*=15.9 Hz), 5.93 (dd, 1H, *J*=7.0, 15.9 Hz), 4.66 (apparent q, 1H), 4.40 (t, 2H, *J*=10.1 Hz), 4.18 (dd, 1H, *J*=6.3, 8.2 Hz), 3.66 (dd, 1H, *J*=7.4, 8.2 Hz), 3.08 (t, 2H, *J*=10.1 Hz), 1.46 (s, 3H), and 1.42 (s, 3H); **4** δ 6.68 (d, 1H, *J*=16.1 Hz), 5.92 (dd, 1H, *J*=5.9, 16.1 Hz), 5.6-5.7 (m, 1H), 4.40 (t, 2H, *J*=10.2 Hz), 4.31 (dd, 1H, *J*=3.9, 11.8 Hz), 4.14 (dd, 1H, *J*=6.5, 11.8 Hz), 3.07 (t, 2H, *J*=10.2 Hz), 2.13 (s, 3H), and 2.08 (s, 3H); **5a** δ 5.72 (d, 1H, *J* =3.4 Hz), 5.27 (dd, 1H, *J* =3.4, 7.2 Hz), 4.2-4.5 (m, 3H), 4.05 (dd, 1H, *J*= 6.2, 8.7 Hz), 3.86 (dd, 1H, *J*= 5.4, 8.7 Hz), 2.9-3.1 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 1.41 (s, 3H), and 1.34 (s, 3H); **5b** δ 5.78 (d, 1H, *J* =6.1 Hz), 5.36 (dd, 1H, *J* = 4.3, 6.1 Hz), 4.2-4.4 (m, 3H), 4.03 (dd, 1H, *J*= 6.8, 8.8 Hz), 3.87 (dd, 1H, *J*=5.1, 8.8 Hz), 3.04 (m [apparent t], 2H, *J*=10.1 Hz), 2.13, 2.12 (2S, 6H), 1.43 (s, 3H), and 1.32 (s, 3H); **6a** δ 5.78 (d, 1H, *J* =3.4 Hz), 5.51 (dd, 1H, *J* =3.4, 8.2 Hz), 5.25 (m, 1H), 4.1-4.5 (m, 4H), 2.9-3.1 (m, 2H), 2.14, 2.12 (2s, 6H), and 2.09, 2.08 (2s, 6H); **6b** δ 5.76 (d, 1H, *J* =6.4 Hz), 5.56 (dd, 1H, *J* = 4.5, 6.4 Hz), 5.31 (m, 1H), 4.3-4.4 (m, 3H), 4.03 (dd, 1H, *J*=6.1, 11.9 Hz), 2.9-3.1 (m [apparent td], 2H), 2.13, 2.12, 2.11 (3s, 9H), and 2.06 (s, 3H).

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10. Other typical conditions which were employed: 0.4 mole equivalent of the chiral auxilliary and double the volume of both water and *t*-BuOH. In one case (Table 1, entry 7) less of the chiral auxilliary was tried: 0.08 mole equivalent worked as well as 0.4 mole equivalent. A referee suggested that the increased requirement for $K_2OsO_4{\cdot}2H_2O$ may be due to Os chelation at the *N*-atom of the DHI resulting in a low catalyst turnover rate.

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