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Synthesis of Homochiral Dihydroxy-4-nitroisoxazolines via One-Pot Asymmetric Dihydroxylation−Reduction

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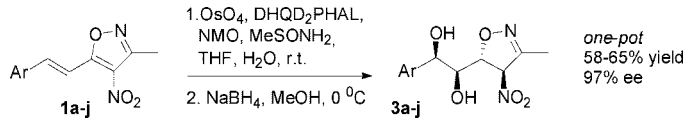
ABSTRACT



Herein we report a one-pot procedure to prepare a family of homochiral dihydroxy-4-nitroisoxazolines 3. This new methodology affords the title compounds in good yields, excellent enantiopurity, and without the use of chromatography.

4-Nitro-5-styrylisoxazoles **1** (Scheme 1) have emerged as useful building blocks for the synthesis of medicinally relevant compounds including propionic acids[1–4] and novel heterocycles.[5–7] As a part of our ongoing efforts in developing one-pot procedures to access families of small bioactive molecules, we envisaged that styrylisoxazoles of general structure **1** could serve as starting materials for the preparation of Δ^2 isoxazolines **3** and polyaminoalcohols **6**. Compounds **6** have shown a rich medicinal chemistry[8] and have been used as precursors for the preparation of pyrrolidines,[9] piperidines,[10] aminosugars,[11] or complex natural products.[12] In our plan, compounds **1** would be submitted to a prelimi-

Scheme 1. Retrosynthetic Analysis of Targets **6**

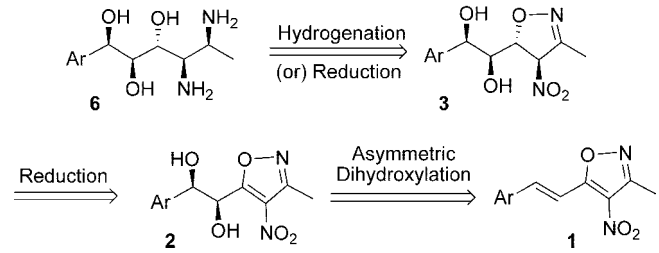


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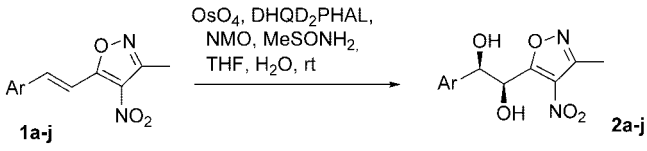
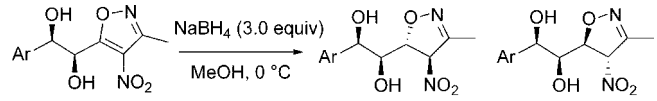
Table 1. Synthesis of Compounds **2a**−**j**



entry	product	Ar	yield %[a]	ee %
1	**2a**	C_6H_5	95	92[c]
2	**2b**	4-F-C_6H_4	96	88[c]
3	**2c**	4-Cl-C_6H_4	98	
4	**2d**	3,4-(OCH_3)-C_6H_3	93	
5	**2e**	3-CH_3-C_6H_4	96	94[c]
6	**2f**	4-(OCH_3)-C_6H_4	96	94[b]
7	**2g**	4-NO_2-C_6H_4	95	92[c]
8	**2h**	2-Cl-C_6H_4	97	94[b]
9	**2i**	4-CN-C_6H_4	97	
10	**2j**	2-naphthyl	90	80[c]
11	**2k**	3-indolyl	75[d]	
12	**2l**	2-furyl		

[a] Isolated yields. [b] Determined using Chiral HPLC analysis using a Chiralcel-AD column, 10% isopropanol in *n*-heptane as an eluent. [c] Determined using Chiral HPLC analysis using a Chiralcel-OJ column, 10% isopropanol in *n*-heptane as an eluent. [d] Obtained using 1 equiv of OsO_4 in pyridine.

Table 2. Isolated Yields of **3a**−**j** and **4a**−**j**



entry	reactant	Ar	% yield of **3**[a]	% yield of **3**[b]	% yield of **4**[b]
1	**2a**	C_6H_5	61	15	20
2	**2b**	4-F-C_6H_4	63	18	16
3	**2c**	4-Cl-C_6H_4	62	14	16
4	**2d**	3,4-(OCH_3)-C_6H_3	61	15	20
5	**2e**	3-CH_3-C_6H_4	63	15	15
6	**2f**	4-(OCH_3)-C_6H_4	61	16	14
7	**2g**	4-NO_2-C_6H_4	65	14	18
8	**2h**	2-Cl-C_6H_4	62	14	10
9	**2i**	4-CN-C_6H_4	62	11	12
10	**2j**	2-naphthyl	58	13	18

[a] Yields obtained after filtration. [b] Yields obtained from the mother liquor using column chromatography.

nary Sharpless asymmetric dihydroxylation[13] and the resulting dihydroxyisoxazoles **2** converted to dihydroxyisoxazolines **3** by partial reduction of the 4-nitroisoxazole core. In this context, the Sharpless dihydroxylation reaction would serve as a means to functionalize the exocyclic alkene in **1** and to set the absolute stereochemistry in the final compounds **6**. We have extensively studied the reactivity of 4-nitro-5-styrylisoxazoles toward nucleophiles.[1–7] On the basis of these studies, we anticipated the 4-nitroisoxazole moiety in **2** would undergo reaction to give Δ^2 isoxazolines **3** when reacted with a suitable metal hydride. Δ^2 Isoxazolines are medicinally relevant compounds that possess a plethora of biological activities including antibacterial,[14] antiplatelet,[15] antiviral,[16] anticonvulsant,[17] immunostimulatory,[18] and antihypertensive.[19] Δ^2 Isoxazolines are also valuable building blocks for the preparation of β-hydroxy carbonyls or β-aminoalcohols.[20] The conventional method of preparation of Δ^2 isoxazolines involves a 1,3-dipolar cycloaddition of nitrile oxides to alkenes. This reaction is highly regioselective. However, high asymmetric induction could be observed only when chiral alkenes were used.[21] For this reason, the development of alternative and practical methods for the preparation of functionalized Δ^2 isoxazolines continues to be an attractive subject of research.[22,23] In this context, we decided to develop a one-pot procedure to convert isoxazoles **1** to Δ^2 isoxazolines **3** that involved sequential dihydroxylation–reduction. Considering that compounds **1** could be easily prepared from commercially available 3,5-dimethyl-4-nitroisoxazole and an aromatic aldehyde,[24] this procedure would furnish a rapid and practical entry to potentially bioactive compounds. It was recognized that dihydroxylation and reduction could be run in one pot provided that (a) conversion of **2** to **3** does not require protection of the hydroxyls; (b) the reducing agent is compatible with the presence of small quantities of OsO_4. In order to find an optimal set of conditions, the conversions of **1** to **2** (Table 1) and of **2** to **3** (Table 2) were independently studied.

In a test experiment, we reacted 5-styryl-4-nitroisoxazole **1a** (Table 1) with a catalytic amount of OsO_4 (0.05 equiv), $DHQD_2Phal$ (0.1 equiv), and an excess (2.2 equiv) of *N*-methylmorpholine (NMO).

Under these conditions, dihydroxyisoxazole **2a** was obtained in high yield and enantioselectivity (Table 1, entry 1). The conversion of **1a** to **2a** was studied in various solvents including pyridine and mixtures of $^tBuOH/H_2O$, $EtOH/H_2O$, $MeOH/H_2O$, $(CH_3)_2CO/H_2O$, and THF/H_2O. This study identified mixtures of THF/H_2O (10:1 or 20:1) as the optimal medium. Similarly, 4-nitro-5-styrylisoxazoles **1b**−**j** containing a substituted phenyl ring were converted to the corre-

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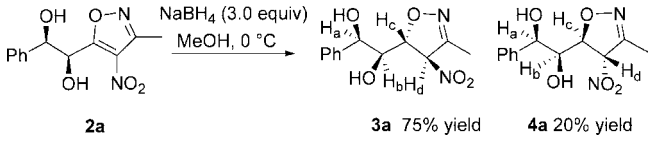
Scheme 2. Reduction of Compounds **2a**



sponding diols **2b**−**j** (Table 1). 4-Nitro-5-styrylisoxazoles **1k**−**l** bearing an aromatic heterocycle failed to give the desired diols **2k**−**l**. In particular, the indolyl-substituted 4-nitro-5-styrylisoxazole **1k** was dihydroxylated only in the presence of a stoichiometric amount of OsO_4. The dihydroxylation of **1l** gave a complex reaction mixture.

Having determined a set of conditions to prepare **2a**−**k**, we turned our attention to the synthesis of isoxazolines **3**. $NaBH_4$ was selected as the reducing agent since (a) this hydride is compatible with the presence of free alcohols and does not require alcohol protection, (b) the 4-nitroisoxazolyl core is prone to react with mild nucleophiles; less reactive 4-carbethoxyisoxazoles also underwent reduction when treated with $NaBH_4$.[21] In a preliminary test, compound **2a** was reacted with $NaBH_4$ (3.0 equiv) in MeOH. Under these conditions, a complete conversion of **2a** occurred and isoxazolines **3a** and **4a** were obtained in 75 and 20% yields, respectively (Scheme 2).

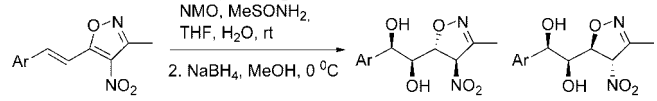
The structure of the major product **3a** was elucidated by X-ray analysis. The structure of **4a** was identified by comparison of its ^{1}H NMR, ^{13}C NMR, and NOE data with those of **4a**. In particular, in compound **3a**, NOE enhancement was noted between H_b and H_d, while in compound **4a**, NOE enhancements were noted between H_a and H_b and between H_b and H_c; this latter one being determinant for the stereochemical assignment.

The preferential formation of compound **3a** over **4a** could be explained by a chelation control exerted by the alcohol functionalities present in **2a**. Hence, formation of compound **3a** occurred by delivery of hydride to the more hindered face of the isoxazole. We have briefly investigated the effect of temperature and rate of addition of $NaBH_4$ on the ratio **3a**:**4a**, but we have noted only small variations. The relative stereochemistry of the two stereogenic centers formed on the Δ^2 isoxazoline ring was exclusively *trans*.

Diols **2b**−**j** were submitted to reaction with $NaBH_4$, and the correspondent Δ^2 isoxazolines **3b**−**j** and **4b**−**j** were obtained in high isolated yields (Table 2).

Notably, compounds **3a**−**j** were obtained pure without the use of chromatography. It was noted that compound **3a** precipitated at the end of the reaction by means of an aqueous acidic workup (Table 2). A sample of **3a** was analyzed by chiral HPLC, and its enantiomeric purity was determined as 97% ee. Compounds **3b**−**j** behaved similarly and were isolated in good yields (Table 2). The ease of purification of **3a**−**j** rendered their preparation operationally simple and practical. The isomeric **4a**−**j** were purified by flash chromatography together with an additional amount of **3a**−**j** present in the mother liquor.

Table 3. One-Pot Synthesis of **3a**−**j** and **4a**−**j**



entry	reactant	Ar	% yield of **3**[a]	% yield of **3**[b]	% yield of **4**[b]
1	**1a**	C_6H_5	63	11	15
2	**1b**	4-F-C_6H_4	61	14	13
3	**1c**	4-Cl-C_6H_4	58	12	12
4	**1d**	3,4-(OCH_3)-C_6H_3	63	13	15
5	**1e**	3-CH_3-C_6H_4	65	12	14
6	**1f**	4-(OCH_3)-C_6H_4	62	13	12
7	**1g**	4-NO_2-C_6H_4	65	11	16
8	**1h**	2-Cl-C_6H_4	64	15	5
9	**1i**	4-CN-C_6H_4	61	12	11
10	**1j**	2-naphthyl	57	10	15

[a] Yields obtained after filtration. [b] Yields obtained from the mother liquor using column chromatography.

Importantly, it was confirmed that the dihydroxylation of **1a**−**j** to obtain **2a**−**j** and the subsequent reduction to Δ^2 isoxazolines **3a**−**j** could be performed in one pot (Table 3). Compounds **1a**−**j** were first submitted to dihydroxylation and then, upon disappearance of starting material, treated with a solution of $NaBH_4$ in methanol. This procedure furnished compounds **3a**−**j** and **4a**−**j** in high yields and in a diastereoisomeric ratio similar to that of the stepwise process (Table 3).

Isoxazolines **3a**−**j** and **4a**−**j** constitute two classes of versatile synthons that could be employed for the preparation of other compounds.[25] In order to evaluate their potential in synthesis, we have submitted compound **3c** to reaction with several reducing agents. Isoxazoline **3c** was therefore reacted with Pd/C and H_2,[26] Zn^0/HCl,[27] $Mo(CO)_6$,[28] $NaBH_4$, and $LiAlH_4$ under several reaction conditions. These experiments furnished a complex reaction mixture in which imine **5c** (Table 4) was obtained contaminated by several side products. The reaction of **3c** with excess Zn^0/CH_3COOH[29] furnished iminoalcohol **5c** in high isolated yield and as a single diastereoisomer (Table 4). The identity of compounds **5** was confirmed by ^{13}C NMR and by 2D NMR studies carried out on compound **5f**. In particular, one signal is present in the ^{13}C NMR of compounds **5f** at ca. 159 ppm that is a quaternary carbon. Additionally, in the HMBC-NMR spectrum, a resonance occurred between the protons of the methyl group (1.87 ppm) and the carbon of the imine (159 ppm).[30]

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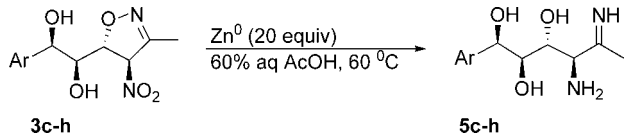
Table 4. Yields of Iminoalcohols **5c**−**h**



3c-h 5c-h

entry	reactant	Ar	product	% yield of **5**[a]
1	**3c**	4-Cl-C_6H_4	**5c**	76
2	**3d**	3,4-(OCH_3)-C_6H_3	**5d**	62
3	**3e**	3-CH_3-C_6H_4	**5e**	54
4	**3f**	4-(OCH_3)-C_6H_4	**5f**	68
5	**3h**	2-Cl-C_6H_4	**5h**	80

[a] Isolated yield after chromatography.

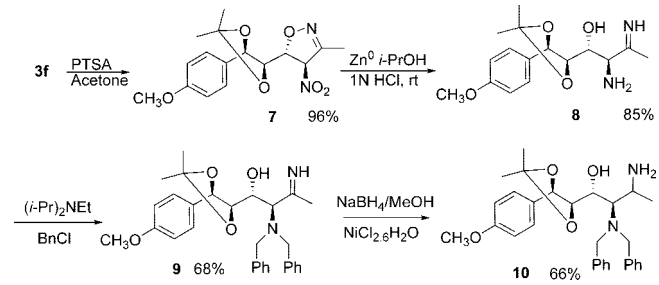
This latter proved unequivocally that in **5f** the CH_3 is bound to an sp^2 quaternary carbon. Isoxazolines **3c**−**h** reacted similarly to afford iminoalcohols **5c**−**h** in high yields (Table 4).

Compounds **5c**−**h** showed a remarkable resistance to reduction and were recovered unreacted after treatment with $NaCNBH_3$, Zn/NaOH, or Zn/Zn(TfO)$_2$. Reaction of **5c** with $LiAlH_4$ or hydrogenolysis in the presence of Pd/C gave a complex mixture of compounds. It is possible that in compounds **5** a hydrogen bond is formed between the imine and the vicinal hydroxyls that is responsible for their exceptional stability.

Imine **9** (Scheme 3), in which two hydroxyls and the amine were protected, underwent fast and efficient reduction when treated with $NaBH_4$ in the presence of $NiCl_2{\cdot}H_2O$. The identity of compound **10** was confirmed by ^{13}C NMR and by 2D NMR. In particular, in the ^1H NMR, a doublet at 0.92 ppm integrating for 3H (CH_3) and a multiplet at 3.16 ppm integrating for 1H ($_2HNC\underline{H}CH_3$) are present. The doublet at 0.92 ppm and the multiplet at 3.16 ppm resonate in the H−H COSY. We have attempted to elucidate the stereochemistry of the newly formed chiral center in **10** by running NOE studies, but results collected were inconclusive.

(30) The 1D and 2D NMR spectra and a full assignment of ^1H and ^{13}C NMR are included in the Supporting Information.

Scheme 3. Synthesis of Compound **10**



In conclusion, we have developed a practical one-pot dihydroxylation−reduction procedure that afforded homochiral Δ^2-isoxazolines **3a**−**j** in good yields and without the use of column chromatography. The synthetic potential of compounds **3** was then explored, identifying an efficient methodology to generate enantiopure iminoalcohols **5c**−**h**. A strategy to obtain protected polyaminoalcohols **10** was also described. Applications of this synthetic strategy to the preparation of natural bioactive compounds are in progress.

Acknowledgment. We would like to acknowledge PTRLI cycle III for a grant to M.F.A.A. and the Health Research Board (HRB) for financial support to M.N.

Supporting Information Available: General procedures for the preparation of compounds **2a**−**j** (Table 1), **3a**−**j**, and **4a**−**j** (Table 2) and for compounds **5c**−**h** (Table 4); procedure for the one-pot preparation of compounds **3a**−**j** and **4a**−**j** (Table 3). Spectroscopic data and copies of ^1H NMR and ^{13}C NMR for compounds **2a**−**j**, **3a**−**j**, **4a**−**j**, **5c**−**f** and **5h**, **7**, **8**, **9**, and **10**; chiral HPLC chromatograms of compounds **2a**−**j**; chiral HPLC chromatogram of **3a** acetonide; X-ray diagram of compound **3a**; 2D NMR, HMBC-NMR, and HMQC-NMR of compound **5f** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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