

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

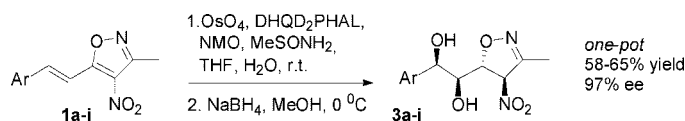
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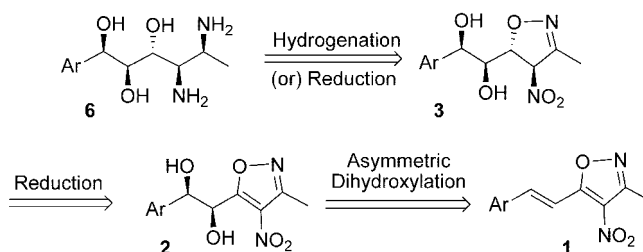
ABSTRACT



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 medically 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 chemistry⁸ and have

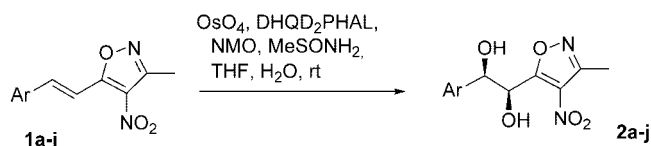
Scheme 1. Retrosynthetic Analysis of Targets **6**



- (1) Adamo, M. F. A.; Duffy, E. F. *Org. Lett.* **2006**, *8*, 5157–5159.
- (2) Adamo, M. F. A.; Konda, V. R. *Org. Lett.* **2007**, *9*, 303–305.
- (3) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2047.
- (4) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *Tetrahedron* **2007**, *63*, 2684.
- (5) (a) Adamo, M. F. A.; Chimichi, S.; De Sio, F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron Lett.* **2002**, *43*, 4157–4160. (b) Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *J. Org. Chem.* **2005**, *70*, 8395–8399.
- (6) Adamo, M. F. A.; Nagabelli, M. *Tetrahedron Lett.* **2007**, *48*, 4703–4706.
- (7) Adamo, M. F. A.; Konda, V. R.; Donati, D.; Sarti-Fantoni, P.; Torroba, T. *Tetrahedron* **2007**, *63*, 9741–9745.
- (8) (a) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matsuzaki, M.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259. (b) Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1978**, *31*, 636. (c) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97.

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-

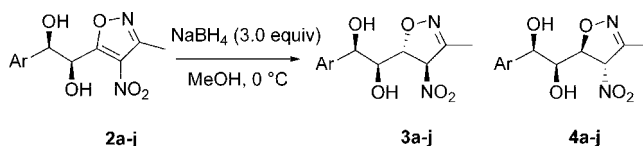
- (9) (a) Setoi, H.; Kayakiri, H.; Takeno, H.; Hashimoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 3995–3999. (b) Fleet, G. W. J.; Son, J. C.; Green, D. C.; Bello, I. C.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649–2655. (c) Ikota, N.; Hanaki, A. *Chem. Pharm. Bull.* **1989**, *37*, 1087–1089.
- (10) Marwenna, S. M. P.; Monique, M. A.; Valerie, F.; Jacques, L. *Eur. J. Org. Chem.* **2005**, *11*, 2159–2191.
- (11) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241–248.
- (12) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561.

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

entry	product	Ar	yield % ^a	ee %
1	2a	C ₆ H ₅	95	92 ^c
2	2b	4-F-C ₆ H ₄	96	88 ^c
3	2c	4-Cl-C ₆ H ₄	98	
4	2d	3,4-(OCH ₃)-C ₆ H ₃	93	
5	2e	3-CH ₃ -C ₆ H ₄	96	94 ^c
6	2f	4-(OCH ₃)-C ₆ H ₄	96	94 ^b
7	2g	4-NO ₂ -C ₆ H ₄	95	92 ^c
8	2h	2-Cl-C ₆ H ₄	97	94 ^b
9	2i	4-CN-C ₆ H 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 OsO₄ in pyridine.

nary Sharpless asymmetric dihydroxylation¹³ 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

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 ₆ H ₅	61	15	20
2	2b	4-F-C ₆ H ₄	63	18	16
3	2c	4-Cl-C ₆ H ₄	62	14	16
4	2d	3,4-(OCH ₃)-C ₆ H ₃	61	15	20
5	2e	3-CH ₃ -C ₆ H ₄	63	15	15
6	2f	4-(OCH ₃)-C ₆ H ₄	61	16	14
7	2g	4-NO ₂ -C ₆ H ₄	65	14	18
8	2h	2-Cl-C ₆ H ₄	62	14	10
9	2i	4-CN-C ₆ H 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.

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 OsO₄. 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 OsO₄ (0.05 equiv), DHQD₂Phal (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/H₂O, EtOH/H₂O, MeOH/H₂O, (CH₃)₂CO/H₂O, and THF/H₂O. This study identified mixtures of THF/H₂O (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-

(13) Hartmuth, C.; Kolb, M.; VanNieuwenhze, S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(14) Kang, Y. K.; Shin, K. J.; Yoo, K. H.; Seo, K. J.; Hong, C. Y.; Lee, C.; Park, S. Y.; Kim, D. J.; Park, S. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 95–103.

(15) Xue, C.; Roderick, J.; Mousa, S.; Olson, R. E.; DeGrado, W. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3499–3509.

(16) Diana, G. D.; McKinlay, M. A.; Brisson, C. J.; Zalay, E. S.; Miralles, J. V.; Salvador, U. J. *J. Med. Chem.* **1985**, *28*, 748–759.

(17) Lepage, F.; Tombert, F.; Cuvier, G.; Marivain, A.; Gillardin, J. M. *Eur. J. Med. Chem.* **1992**, *27*, 581–588.

(18) Ryn, S.; Machon, Z.; Wieczorek, Z.; Zimecki, M.; Mokrosz, M. *Eur. J. Med. Chem.* **1998**, *33*, 831–835.

(19) Dallanocce, C.; Meroni, G.; De Amici, M.; Hoffman, C.; Klotz, K.-N.; De Micheli, C. *Bioorg. Med. Chem.* **2006**, *14*, 4393–4401.

(20) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587–1590.

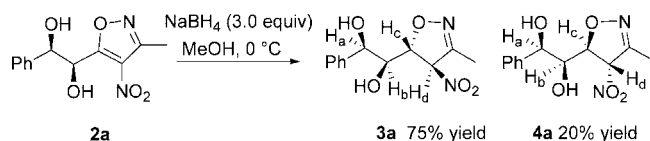
(21) Lee, C. K. Y.; Herlt, A. J.; Simpson, G. W.; Willis, A. C.; Easton, C. J. *J. Org. Chem.* **2006**, *71*, 3221–3231.

(22) Kumar, R. R.; Perumal, S. *Tetrahedron* **2007**, *63*, 12220–12231.

(23) Kaffy, J.; Pontikis, R.; Carrez, D.; Croisy, A.; Monneret, C.; Florent, J.-C. *Bioorg. Med. Chem.* **2006**, *14*, 4067–4077.

(24) Adamo, M. F. A.; Duffy, E. F.; Konda, V. R.; Murphy, F. *Heterocycles* **2007**, *71*, 1173–1181.

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 OsO₄. 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**. NaBH₄ 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-carbomethoxyisoxazoles also underwent reduction when treated with NaBH₄.²¹ In a preliminary test, compound **2a** was reacted with NaBH₄ (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).

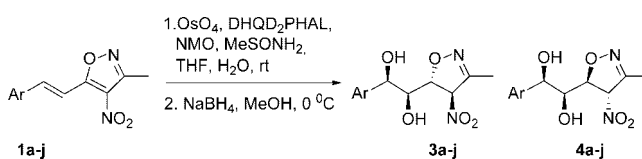
The structure of the major product **3a** was elucidated by X-ray analysis. The structure of **4a** was identified by comparison of its ¹H NMR, ¹³C NMR, and NOE data with those of **4a**. In particular, in compound **3a**, NOE enhancement was noted between H_b and H_d, while in compound **4a**, NOE enhancements 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 NaBH₄ on the ratio **3a**:**4a**, but we have noted only small variations. The relative stereochemistry of the two stereogenic centers formed on the Δ² isoxazoline ring was exclusively *trans*.

Diols **2b–j** were submitted to reaction with NaBH₄, and the correspondent Δ² 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 ₆ H ₅	63	11	15
2	1b	4-F-C ₆ H ₄	61	14	13
3	1c	4-Cl-C ₆ H ₄	58	12	12
4	1d	3,4-(OCH ₃)-C ₆ H ₃	63	13	15
5	1e	3-CH ₃ -C ₆ H ₄	65	12	14
6	1f	4-(OCH ₃)-C ₆ H ₄	62	13	12
7	1g	4-NO ₂ -C ₆ H ₄	65	11	16
8	1h	2-Cl-C ₆ H ₄	64	15	5
9	1i	4-CN-C ₆ H 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 Δ² 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 NaBH₄ 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 H₂,²⁶ Zn⁰/HCl,²⁷ Mo(CO)₆,²⁸ NaBH₄, and LiAlH₄ 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 Zn⁰/CH₃COOH²⁹ furnished iminoalcohol **5c** in high isolated yield and as a single diastereoisomer (Table 4). The identity of compounds **5** was confirmed by ¹³C NMR and by 2D NMR studies carried out on compound **5f**. In particular, one signal is present in the ¹³C 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

(25) Patrick, A.; Lisbet, K.; Roger, W. G.; Florian, K.; Carreira, E. M. *Org. Lett.* **2005**, 7, 5741–5742.

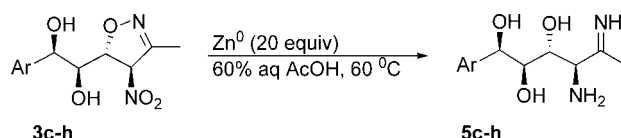
(26) Caplan, J. F.; Zheng, R.; Blanchard, J. S.; Vedeiras, J. C. *Org. Lett.* **2000**, 2, 3857–3860.

(27) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, 69, 1262–1269.

(28) (a) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Chem. Commun.* **1982**, 877–878. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Guarneri, M.; Manfredini, S.; Pillini, G. P.; Simoni, D. *Tetrahedron Lett.* **1985**, 26, 5319–5322.

(29) (a) Watanabe, Y.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, 54, 4088–4097. (b) Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, 5, 391–394. (c) Lepore, S. D.; Schacht, A. L.; Wiley, M. R. *Tetrahedron Lett.* **2002**, 43, 8777–8779.

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



entry	reactant	Ar	product	% yield of 5^a
1	3c	4-Cl-C ₆ H ₄	5c	76
2	3d	3,4-(OCH ₃)-C ₆ H ₃	5d	62
3	3e	3-CH ₃ -C ₆ H ₄	5e	54
4	3f	4-(OCH ₃)-C ₆ H ₄	5f	68
5	3h	2-Cl-C ₆ H ₄	5h	80

^a Isolated yield after chromatography.

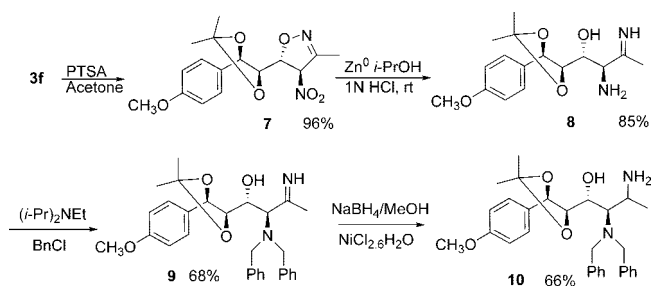
This latter proved unequivocally that in **5f** the CH₃ is bound to an sp² quaternary carbon. Isoxazolines **3c–h** reacted similarly to afford iminoalcohols **5c–h** in high yields (Table 4).

Compounds **5c–h** showed a remarkable resistance to reduction and were recovered unreacted after treatment with NaCNBH₃, Zn/NaOH, or Zn/Zn(TfO)₂. Reaction of **5c** with LiAlH₄ 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 NaBH₄ in the presence of NiCl₂·H₂O. The identity of compound **10** was confirmed by ¹³C NMR and by 2D NMR. In particular, in the ¹H NMR, a doublet at 0.92 ppm integrating for 3H (CH₃) and a multiplet at 3.16 ppm integrating for 1H (2HNCHCH₃) 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 ¹³C 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 homo-chiral Δ²-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.

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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 ¹³C 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** acetone; 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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