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Novel enantiomerically pure 2-amino-1,4-diols from chiral 4-hydroxymethyl-5-iodo-1,3-oxazin-2-ones

M. Eugenia González-Rosende,[a,*] J. Miquel Jordá-Gregori,[b] José Sepúlveda-Arques[b] and Mario Orena[c]

[a]*Departamento de Química, Bioquímica y Biología Molecular, Facultad de Ciencias Experimentales y de la Salud, Universidad Cardenal Herrera-CEU, Edificio Seminario, 46113 Moncada, Valencia, Spain*
[b]*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Avda. Vicent Andres Estelles s/n, 46180 Burjassot, Valencia, Spain*
[c]*Dipartimento di Scienze dei Materiali e della Terra, University of Ancona, Via Brecce Bianche, I-60131 Ancona, Italy*

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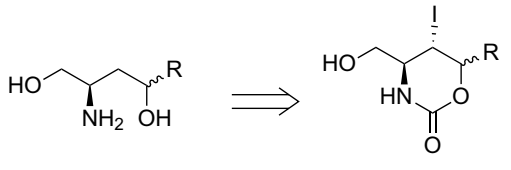
Abstract—Reduction of (4*S*,5*S*,6*S*)-4-hydroxymethyl-5-iodo-6-methyl-1,3-oxazin-2-one **2a** and (4*S*,5*S*,6*R*)-4-hydroxymethyl-5-iodo-6-phenyl-1,3-oxazin-2-one **2b** with tributyltin hydride in ethanol afforded 1,3-oxazin-2-one **3a** and 1,3-oxazolidin-2-one **4b**, respectively. Hydrolysis of **3a** and **4b** under basic conditions led to enantiomerically pure aminodiols **1a** and **1b**. Reduction of **2b** in refluxing toluene led to the unexpected bicyclic tetrahydrofuro[3*a*,*d*]-1,3-oxazolidin-2-one **5** as the sole product.

1. Introduction

Optically active amino diols are of interest for the chiral pool and as partial structures of biologically active compounds.[1] Within a project aimed to prepare amino polyols with high stereoselection, we considered that 2-amino-1,4-diols **1** could be obtained from chiral 4-hydroxymethyl-5-iodo-1,3-oxazin-2-ones **2** (Scheme 1). Thus, we report herein the preparation of 2-amino-1,4-diols **1a** and **1b** in the enantiomerically pure form.



1 **2**

1a R = CH_3 conf. *S*
1b R = Ph conf. *S*

Scheme 1.

2. Results and discussion

The starting materials for our study were 4-hydroxymethyl-5-iodo-1,3-oxazin-2-ones **2a** and **2b**, easily obtained from Garner's aldehyde[2] following highly regio and stereoselective iodocyclocarbamation reactions of *N*-Boc and *N*-Cbz allylic carbamates.[3] Although these cyclocarbamation reactions followed by tributyltin hydride mediated dehalogenation are common synthetic processes,[4] both oxazinones **2** showed a new behaviour in the reduction pathway. In fact, when 5-iodo-1,3-oxazin-2-one **2a** was treated in refluxing ethanol or toluene in the presence of azo-*bis*-isobutyronitrile (AIBN), the corresponding dehalogenated oxazinone **3a**, along with 1,3-oxazolidin-2-one **4a** were obtained, this latter compound reasonably arising from an intramolecular transcarbamation reaction (Scheme 2).[5] This rearrangement process probably occurs via formation of a nucleophilic tin alkoxide since when pure compound **3a** was heated in refluxing ethanol, the formation of oxazolidinone **4a** was not observed. Although analogous oxazolidinone formation due to the nucleophilic attack onto a neighbouring carbamate by an alkoxide anion obtained via sodium hydride treatment has previously been reported in the literature,[6] to the best of our knowledge there are no published reports on such reactions carried out with tin hydride reagents.

* Corresponding author. E-mail: eugenia@uch.ceu.es

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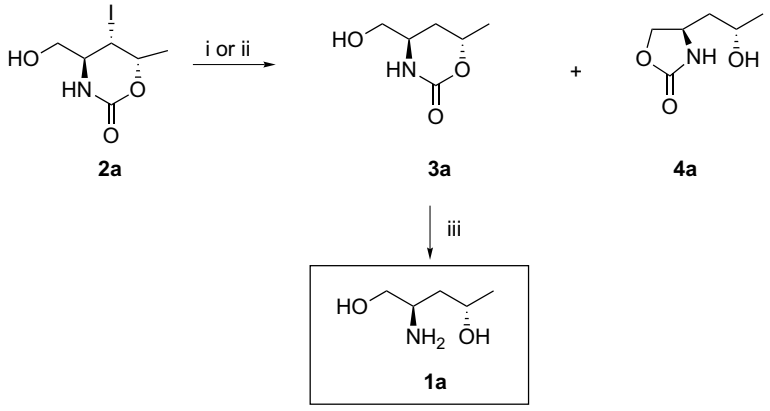
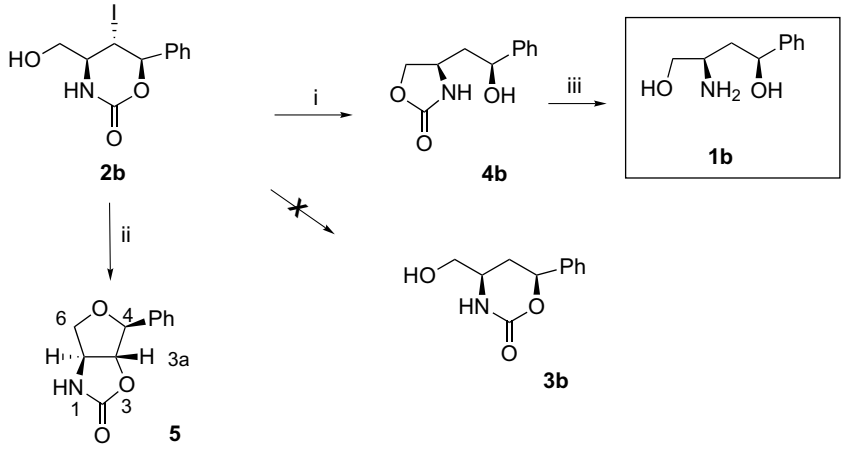


Scheme 2. Reagents, conditions and yields: (i) Bu_3SnH/AIBN/refluxing EtOH: **3a** (40%), **4a** (22%); (ii) Bu_3SnH/AIBN/refluxing toluene: **3a** (25%), **4a** (14%); (iii) 5 M NaOH: **1a** (71%).

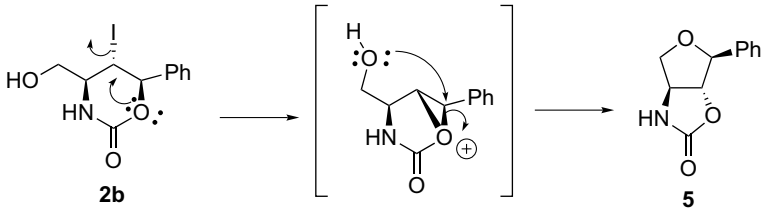
Oxazinone **3a** was successfully hydrolyzed to afford the enantiopure amino diol (2*R*,4*S*)-2-amino-pentane-1,4-diol **1a**.

Different results, however, were observed when 1,3-oxazin-2-one **2b**, having a phenyl substituent at C-6, underwent reductive cleavage of the C–I bond (Scheme 3). Thus, treatment of compound **2b** with tributyltin hydride in refluxing ethanol, gave exclusively the corresponding rearranged 1,3-oxazolidin-2-one **4b** in good yield and the expected deiodinated 1,3-oxazin-2-one **3b** could not be detected. Cleavage of the oxazolidinone ring of compound **4b** by hydrolysis under basic classical conditions afforded the corresponding amino diol (1*S*,3*R*)-3-amino-1-phenylbutane-1,4-diol **1b**. A rather surprising result was observed when the reduction of oxazinone **2b** was carried out in boiling toluene instead of ethanol. In this case, the bicyclic carbamate **5** was exclusively obtained. To the best of our knowledge, only one example of an analogous carbamate rearrangement process has been described in the literature.[7]

A possible mechanism describing the formation of compound **5** is shown in Scheme 4.



Scheme 3. Reagents, conditions and yields: (i) Bu_3SnH/AIBN/refluxing EtOH: **4b** (72%); (ii) Bu_3SnH/AIBN/refluxing toluene: **5** (35%); (iii) 5 M NaOH: **1b** (65%).



Scheme 4.

The structural assignment of oxazinone **3a** and oxazolidinones **4a** and **4b** was performed on the basis of their spectral data. In fact, the observed carbonyl absorption of both **4a** and **4b** at 1743 and 1731 cm^{-1}, respectively, was diagnostic for a five-membered ring carbamate,[8] whereas oxazinone **3a** showed carbonyl absorption at 1706 cm^{-1} in agreement with the literature data.[9] In addition, inspection of the ^{13}C NMR spectra clearly showed the downfield shift of the carbonyl resonance in **4a** and **4b** (161.0, 159.9 ppm, respectively) and the upfield shift of the carbonyl in **3a** (156.1 ppm) according to the literature.[10] Eventually, the structure of oxazolidinones **4a** and **4b** was confirmed by oxidation of compound **4b** to the corresponding ketone **6**, performed using Jones reagent[11] in order to ascertain the presence of a secondary hydroxy function in **4b**. The oxazolidinone ring structure of the bicyclic compound **5** was determined on the basis of the carbonyl stretching band at 1746 cm^{-1} in the IR spectrum, diagnostic for a five-membered ring carbamate.[8,10] In addition, the relative stereochemistry was assigned by inspection of H_{3a} coupling constants values (dd, $J_{H3a-H6a} = 5.1$ Hz and $J_{H3a-H4} = 2$ Hz). In fact, the $J_{H3a-H6a}$ is typical for a *trans*-relationship of a disubstituted oxazolidinone ring[12] and the J_{H3a-H4} value agrees with a H_{3a}–H_4 *trans* coupling in 1,2-disubstituted tetrahydrofurans.[13]

3. Conclusions

In summary, we have reported herein our results on the preparation of enantiomerically pure amino diols **1a** and **1b** with defined configuration and we have shown the synthetic application of a facile new route for the stereoselective synthesis of amino diol derivatives containing multiple stereocentres, starting from easily available chiral compounds as 1,3-oxazin-2-ones **2a** and **2b**.

4. Experimental section

4.1. General methods

All reagents were purchased from Aldrich and used without purification unless stated otherwise. All experiments were made under nitrogen atmosphere. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on a FT-IR spectrometer. Flash column chromatography was performed using silica gel (Merck 60, 70–230 mesh). ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument in $CDCl_3$, unless otherwise indicated. Chemical shifts (δ values relative to tetramethylsilane) and coupling constants (J values) are given in ppm and Hz, respectively. HRMS were obtained using a VG Autospec TRIO 1000 instrument. The ionization mode used in mass spectra was electron impact (EI). Optical rotations were measured at rt on a Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR assignments have been confirmed by homonuclear two-dimensional correlations and DEPT experiments. Compound **2b** was prepared as described in Ref. 3a.

(4*S*,5*S*,6*R*)-4-Hydroxymethyl-5-yodo-6-methyl-1,3-oxazin-2-one **2a**. (4*S*,5*S*,6*S*)-1-Aza-5-iodo-4,9,9-trimethyl-3,8-dioxa-2-oxobyciclo[4.3.0]nonane[3b] (3.11 g, 10 mmol) was dissolved in 95:5 CH_3OH/H_2O (250 mL) containing *p*-toluenesulfonic acid monohydrate (98 mg, 0.5 mmol) and the mixture was refluxed for 18 h. The crude was concentrated, and the residue was purified by flash chromatography on silica gel using gradient elution (hexane/ethyl acetate, 9:1, 4:1, 1:1) to give **2a** (1.84 g) in 68% yield as a white solid. Mp 200–201 °C; $[\alpha]_D = -70$ (*c* 1.08, MeOH); IR (KBr) 3441, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.17 (d, $J = 5.8$, 3H), 3.34–3.42 (m, 3H), 3.58–3.65 (m, 2H), 4.72 (m, 1H), 5.15 (br s, 1H), 7.53 (d, $J = 3.39$, 1H); ^{13}C NMR (DMSO-d_6) δ 22.8 (CH_3), 31.7 (CH), 62.2 (CH), 64.0 (CH_2), 70.2 (CH), 151.2 (C=O); EI-HRMS calcd for $C_6H_{10}INO_3$ $(M)^+$ 270.9705, found 270.9723.

4.2. General procedure for reduction of compounds 2a and 2b

To a solution of the corresponding compound **2** (10 mmol) in dry EtOH (58 mL) or dry toluene (58 mL) was added AIBN (3.28 g, 20 mmol). Then, Bu_3SnH (5.42 mL, 20 mmol) was added dropwise. The reaction mixture was stirred at reflux for 4 h. The solution was concentrated in vacuo and the resultant residue was purified by flash chromatography (hexane/ethyl acetate/methanol with gradient polarity).

(4*R*,6*S*)-4-Hydroxymethyl-6-methyl-1,3-oxazin-2-one **3a**. White solid. Mp 91–94 °C; $[\alpha]_D = -78.7$ (*c* 1, MeOH); IR (CH_2Cl_2) 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (d, $J = 6.2$, 3H), 1.63–1.71 (m, 1H), 1.79–1.84 (m, 1H), 3.50–3.52 (m, 3H), 3.85 (br s, 1H), 4.46–4.51 (m, 1H), 7.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_3), 29.3 (CH_2), 50.1 (CH), 65.4 (CH_2), 71.9 (CH), 156.1 (C=O); EI-HRMS calcd for $C_6H_{11}NO_3$ $(M)^+$ 145.0739, found 145.0737.

(4*R*)-4-[(2*S*)-2-Hydroxypropyl]-1,3-oxazolidin-2-one **4a**. Colourless oil. $[\alpha]_D = +10.9$ (*c* 0.96, MeOH); IR (CH_2Cl_2) 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (d, $J = 6.2$, 3H), 1.50–1.81 (m, 2H), 3.2 (br s, 1H), 3.80–4.1 (m, 3H), 4.48 (dd, $J = 8$, $J = 7$, 1H), 6.9 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3 (CH_3), 44.1 (d, CH_2), 50.4 (CH), 64.9 (CH), 71.4 (CH_2), 161.0 (C=O); EI-HRMS calcd for $C_6H_{11}NO_3$ $(M)^+$ 145.0739, found 145.0733.

(4*R*)-4-[(2*S*)-2-Hydroxy-2-phenylethyl]-1,3-oxazolidin-2-one **4b**. White solid. Mp 98–99 °C; $[\alpha]_D = -8.13$ (*c* 0.96, MeOH); IR (CH_2Cl_2) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (m, 1H), 1.86 (m, 1H), 3.73 (d, $J = 3.3$, 1H), 3.83–3.89 (m, 2H), 4.30 (dd, $J = 8.2$, $J = 7$, 1H), 4.64 (m, 1H), 6.43 (br s, 1H), 7.21 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 43.7 (CH_2), 51.5 (CH), 70.2 (CH_2), 72.6 (CH), 125.5 (CH), 125.6 (CH), 128.5 (CH), 143.8 (C), 159.9 (C=O); EI-HRMS calcd for $C_{11}H_{13}NO_3$ $(M)^+$ 207.0895, found 207.0901.

(3a*R*,4*S*,6a*R*)-4-Phenyltetrahydrofuro[3*a*-*d*][1,3]oxazol-2(3*H*)-one **5**. White solid. Mp 75–78 °C; $[\alpha]_D = +79.7$ (*c* 1.04, MeOH); IR (CH_2Cl_2) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.04 (dd, $J = 5.1$, $J = 2$, 1H), 3.76 (d, $J = 2.0$, 1H), 3.91 (m, 1H), 4.06 (dd, $J = 9.0$, $J = 5.4$, 1H), 4.45 (dd, $J = 9$, $J = 8.6$, 1H), 6.99 (br s, 1H), 7.14 (m, 2H), 7.22 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 53.1 (CH), 56.0 (CH), 62.3 (CH), 66.5 (CH_2), 125.7 (CH), 128.5 (CH), 134.0 (CH), 135.5 (C), 160.0 (C=O); EI-HRMS calcd for $C_{11}H_{11}NO_3$ $(M)^+$ 207.0738, found 207.0731.

(4*R*)-4-(2-Oxo-2-phenylethyl)-1,3-oxazolidin-2-one **6**. To a solution of **4b** (1 g, 4.8 mmol) in acetone (12 mL) cooled at 0 °C was added dropwise freshly prepared 1 M Jones reagent[11] (4 mL, 5.3 mmol). After being stirred at 0 °C for 30 min, the reaction was quenched by addition of isopropanol (9 mL) at the same temperature and stirring was continued for another 30 min. The mixture was decanted and the solution was concentrated to give compound **6** (0.94 mg, 95%) as a white solid. Mp 134–137 °C; IR 3436, 1759, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (m, 1H), 4.06 (dd, $J = 8.0$, $J = 6.0$, 1H), 4.35 (m, 1H), 4.60 (dd, $J = 8.8$, $J = 8.4$, 1H), 6.08 (br s, 1H), 7.41 (dd, $J = 8.3$, $J = 7.3$, 2H), 7.54 (tt, $J = 7.3$, $J = 1.5$, 1H) 7.86 (dd, $J = 8.3$, $J = 1.5$, 2H); ^{13}C NMR ($CDCl_3$) δ 44.0 (CH_2), 48.7 (CH), 70.0 (CH_2), 128.0 (CH), 128.8 (CH), 134.0 (CH), 135.8 (C), 159.3 (C=O), 197.5 (C=O); $[\alpha]_D = 3.9$ (*c* 1, MeOH); EI-HRMS calcd for $C_{11}H_{11}NO_3$ (M^+) 205.0738, found 205.0731.

4.3. Preparation of amino diol derivatives 1a and 1b. General procedure

To a solution containing oxazinone **3a** or oxazolidinone **4b** (10 mmol) in ethanol (25 mL) was added a 5 M solution of NaOH (25 mL) and the mixture was refluxed for 5 h. When the reaction was completed 5% HCl was added. The reaction was then extracted with ethyl acetate and dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane, ethyl acetate and methanol with gradient polarity).

(2*R*,4*S*)-2-Amino-pentane-1,4-diol **1a**. Yield 0.85 g, 71%; $[\alpha]_D = +10.7$ (*c* 1.02, MeOH); ^1H NMR (D_2O) δ 1.05 (d, $J = 6.2$, 3H), 1.40–1.55 (m, 2H), 3.24 (m, 1H), 3.37 (dd, $J = 7.35$, $J = 12.4$, 1H), 3.59 (m, 1H), 3.77 (m, 1H); ^{13}C NMR (D_2O) δ 22.7 (CH_3), 37.2 (CH_2), 50.9 (CH), 61.8 (CH_2), 64.4 (CH), 156.1 (C=O); EI-HRMS calcd for $C_5H_{14}NO_2$ $(MH)^+$ 120.1024, found 120.1016.

(1*S*,3*R*)-3-Amino-1-phenylbutane-1,4-diol **1b**. Yield 1.17 g, 65%; $[\alpha]_D = -3.46$ (*c* 1.04, MeOH); ^1H NMR ($CDCl_3$) δ 1.9–2.2 (m, 5H), 3.7 (dd, $J = 8.85$, $J = 3.75$, 2H), 3.8 (m, 1H), 4.1 (dd, $J = 8.85$, $J = 5.3$, 1H), 5.2 (dd, $J = 8.6$, $J = 6.6$, 1H); ^{13}C NMR ($CDCl_3$) δ 44.8 (CH_2), 52.8 (CH), 64.0 (CH_2), 79.9 (CH), 126.0 (CH), 127.7 (CH), 128.8 (CH), 143.1 (C); EI-HRMS calcd for $C_{10}H_{15}NO_2$ $(M)^+$ 181.1102, found 181.1094.

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