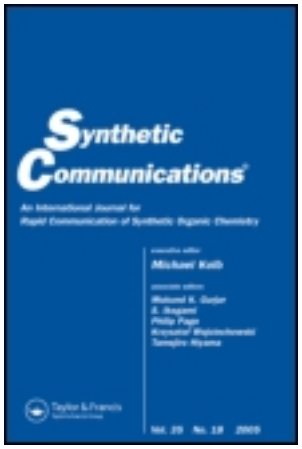

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Enantiomerically Enriched Bicyclic Hydroxamic Acids in One Step from α-Aminohydroxamic Acids and Keto Acids via Cyclocondensation

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ENANTIOMERICALLY ENRICHED BICYCLIC HYDROXAMIC ACIDS IN ONE STEP FROM α-AMINOHYDROXAMIC ACIDS AND KETO ACIDS VIA CYCLOCONDENSATION

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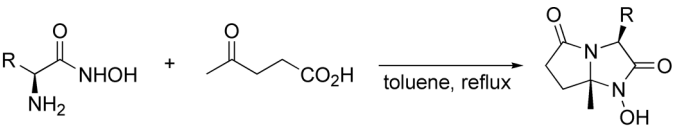
GRAPHICAL ABSTRACT



R = Me, ^{i}Pr, Bn, indolylmethyl, imidazolylmethyl 96–49% yield

Abstract *New enantiomerically enriched bicyclic hydroxamic acids, 1-hydroxy-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, have been synthesized by the cyclocondensation of* L*-α-aminohydroxamic acids with keto acids in a highly chemo- and stereoselective manner. The* cis *configuration between the amino acid side chain and the methyl group at C7a in 1*H*-pyrrolo[1,2-*a*]imidazole-2,5-dione was unambiguously established by X-ray crystallographic analysis. This method could also be applied to the cyclocondensation with* o*-formylbenzoic acid, giving a tricyclic hydroxamic acid in a good yield.*

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Keywords Chiral compounds; cyclocondensation; hydroxamic acids; *N*-hydroxyimidazolidinones; keto acids

INTRODUCTION

Cyclic hydroxamic acids are widely distributed in nature, such as in siderophores, antibiotics, and microbial pigments, and exhibit several biological activities, including inhibitory activities of matrix metalloproteinases, human hypoxia-inducible factor (HIF) prolyl hydroxylase, phosphatase, interleukin IL-1β converting enzyme (ICE), and HIV-1 integrase; antagonistic activity of *N*-methyl-D-aspartate (NMDA)

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receptor; immunosuppressive activity; and antimalarial activity.[1–9] The synthesis of cyclic hydroxamic acids has attracted the attention of many research groups. One interesting area of research is the cyclocondensation reaction of α-aminohydroxamic acids with carbonyl compounds, giving monocyclic hydroxamic acids, 3-hydroxyimidazolidin-4-ones.[10] This cyclocondensation reaction provides a potentially attractive method to stereoselectively prepare the 2,5-disubstituted 3-hydroxyimidazolidin-4-ones, which allows diverse elements to be incorporated at the C2 and C5 positions.

Chiral acyclic hydroxamic acids have recently received increasing attention as chiral ligands in the field of asymmetric transition-metal catalysis such as epoxidation of alkenols,[11] alkenylsulfonamides,[12] or simple olefins,[13] oxidation of sulfides;[14] and reduction of ketones.[15] On the other hand, chiral cyclic hydroxamic acids, to the best of our knowledge, have never been examined as a chiral ligand candidate in asymmetric metal catalysis. The structural diversity of 2,5-disubstituted 3-hydroxyimidazolidin-4-ones makes this compound class convenient for exploration and optimization of chiral cyclic hydroxamic acid ligands and necessitates the development of stereoselective synthesis of such molecules. Although the reaction of glycine hydroxamic acid or some racemic α-aminohydroxamic acids with aldehydes or symmetric ketones have been reported,[10] the examples of diastereoselective cyclocondensation of α-aminohydroxamic acids to 2,5-disubstituted 3-hydroxyimidazolidin-4-ones have been fairly limited and have not indicated the selectivities.[10a-c,h] In addition, the competitive *O*-alkylation of hydroxamic acids may result in the unfavorable formation of 1,2,5-oxadiazinan-3-ones,[10a,16] though *N*-alkylation of amide N-H preferentially occurred in the condensation of α-amino acid phenylhydrazides with levulinic acids and carbonyl compounds.[17] Herein we report the first synthesis of enantiomerically enriched 1-hydroxy-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, a kind of 2,5-substituted 3-hydroxyimidazolidin-4-one derivatives, by means of the cyclocondensation of L-α-aminohydroxamic acids **1a–e** with levulinic acid (**2**) or 5-oxohexanoic acid (**5**), which has a feature that enables the facile combinatorial synthesis of the libraries of chiral cyclic hydroxamic acids from commercially available or easily prepared α-aminohydroxamic acids and carbonyl compounds. The stereochemistry of (3*S*,7a*R*)-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-dione **3a** was unambiguously confirmed by X-ray crystallographic analysis. This method also could be applied to the cyclocondensation of α-aminohydroxamic acids with *o*-formylbenzoic acid (**6**).

RESULTS AND DISCUSSION

L-α-Aminohydroxamic acids **1a–e** were prepared in good yields from their respective methyl esters in a manner similar to the literature procedure.[18] When L-phenylalanine hydroxamic acid (**1a**) was treated with levulinic acid (**2**) in refluxing toluene, the sparingly soluble compound **3a**, which gave a positive (purple) color test with ferric chloride suggesting the presence of a hydroxamic acid function, was obtained in a good yield (Table 1, entry 1). The ^{1}H NMR analysis of the solid **3a** suggested a 1:1 condensation product of **1a** with **2** but elucidation of the structure remained ambiguous. The irradiation of CH_3 group of **3a** caused a positive nuclear Overhause effect (NOE) for the Ar-H and had no effect on the hydrogen atom of CH

Table 1. Cyclocondensation of α-aminohydroxamic acids (**1**) with levulinic acid (**2**)

Entry	1	R^1	Conditions	3	Yield (%)
1	**1a**	$PhCH_2$	Toluene, reflux, 2 h	**3a**	84
2	**1a**		Toluene, reflux, 18 h (Dean-Stark app.)	**3a**	82
3	**1b**	Me	Toluene, 80 °C, 5 h	**3b**	49
4	**1c**	*i*-Pr	Toluene, reflux, 4 h	**3c**	59
5	**1d**	indol-3-ylmethyl	2-Propanol, reflux, 2 h; toluene, reflux, 7 h	**3d**	95
6	**1e**	imidazol-4-ylmethyl	2-Propanol, reflux, 2 h; toluene, reflux, 7 h	**3e**	96

α to the hydroxamic acid moiety (Fig. 1). Similarly, irradiation of the benzylic CH_2 led to a positive NOE for the CH_3. These ^1H NMR data provide evidence for the *cis* stereochemistry of the CH_3 group to the benzyl group. Finally, the structure of cyclic hydroxamic acid **3a** was established by X-ray diffraction analysis (Fig. 2). It is important to note that the reaction proceeded in a highly chemo- and stereoselective manner to give exclusively the *cis* isomer. This stereochemical outcome is comparable to the related cyclization reactions.[17,19] The procedure using a Dean–Stark apparatus is also applicable to the condensation, giving the same results (entry 2).

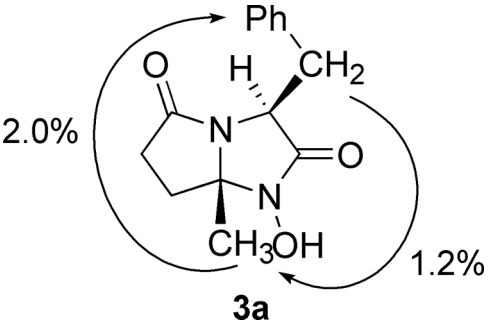


Figure 1. NOE experiment of **3a**.

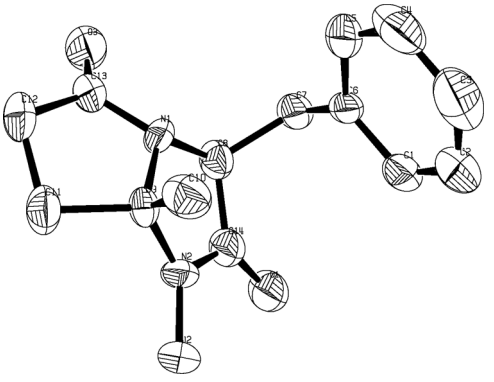
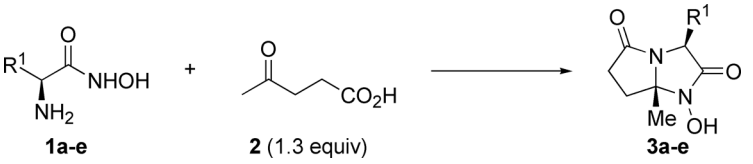


Figure 2. ORTEP diagram of **3a**.



Scheme 1. Cyclocondensation of L-α-aminohydroxamic acids **1** with levulinic acid (**2**).

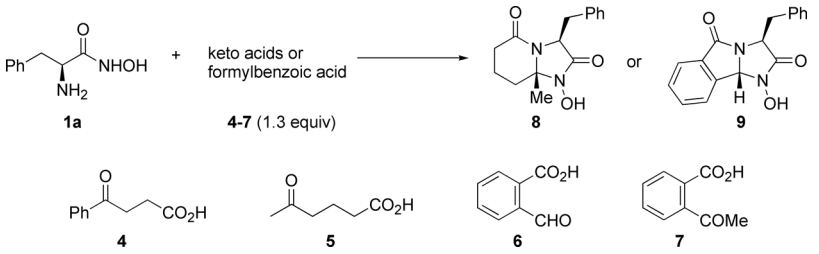
Some representative aminohydroxamic acids were evaluated for cyclocondensation with levulinic acid (Table 1, entries 3–6). Aliphatic aminohydroxamic acids **1b** and **1c** gave the cyclic hydroxamic acids **3b** and **3c** in moderate yields (49–59%). On the other hand, aromatic aminohydroxamic acids **1d** and **1e** were sparingly soluble in toluene and the unknown brown gum substance appeared in the refluxing reaction mixture. Consequently, the condensations of **1d** and **1e** with **2** were carried out in refluxing 2-propanol for 2 h. Then, toluene was added to the reaction mixture, which was heated to 135 °C while 2-propanol and water were distilled off azeotropically with toluene. This method gave the desired cyclic hydroxamic acids **3d** and **3e** in good yields (95–96%). It is noted that all the products obtained show the *cis* configuration of methyl group and side chain of aminoacyl moiety.

Next, the possibility of varying the structure of keto acids was examined (Table 2). Phenyl substituted keto acid **4** was conducted in either toluene or 2-propanol, but the desired phenyl-substituted bicyclic hydroxamic acid was not obtained at all, presumably because the first ring closure or the second cyclization might be suppressed by sterically demanded phenyl group. 5-Oxohexanoic acid (**5**) was condensed with **1a**, affording the corresponding 5-6 bicyclic hydroxamic acid **8** in a good yield.

To expand this method, benzoic acid derivatives were next examined. While the reaction of formylbenzoic acid **6** with aminohydroxamic acid **1a** in the reaction conditions gave poor results (Table 2, entry 2), addition of *p*-toluenesulphonic acid (0.1 equiv) as an acid catalyst improved the yield of **9** (40%). Because the white solid intermediate appeared during the reaction, *o*-xylene (140 °C) was used as solvent to dissolve the solid, but the yield was not improved. After some trials, use of benzene as solvent and Dean–Stark apparatus for azeotropic distillation resulted in a good yield (72%). The absolute configuration of the newly generated chiral center in **9** was determined by NOE experiments. A similar *trans*-orientation of H3 and H9b was reported in the related condensations by Katritzky et al.[20] For the reaction with *o*-acetylbenzoic acid (**7**), the starting material aminohydroxamic acid was

Table 2. Cyclocondensation of L-phenylalanine hydroxamic acid (**1a**) with oxo acids

Entry	Oxo acid	Conditions	Cyclic hydroxamic acid	Yield (%)
1	**5**	Toluene, reflux, 7 h	**8**	67
2	**6**	Toluene, reflux, 20 h	**9**	15
3	**6**	p-TsOH (0.1 equiv), toluene, reflux, 20 h	**9**	40
4	**6**	p-TsOH (0.1 equiv), xylene, reflux, 20 h	**9**	27
5	**6**	p-TsOH (0.1 equiv), benzene, reflux, 20 h	**9**	72



Scheme 2. Cyclocondensation of L-phenylalanine hydroxamic acid (**1a**) with oxo acids.

consumed quantitatively, but complex mixtures were obtained. No desired product was observed in spectroscopic analysis.

In summary, we have demonstrated that the cyclocondensation of L-α-amino-hydroxamic acids with γ- and δ-keto acids afforded optically active, sterically rigid bi- or tricyclic hydroxamic acids in a highly chemo- and stereoselective manner. The simple experimental procedure along with ready accessibility of reactants is also an attractive feature. Application of these cyclic hydroxamic acids to catalytic asymmetric reactions using metal complexes is in progress.

EXPERIMENTAL

Typical Experimental Procedure for the Cyclocondensation of L-α-Aminohydroxamic Acids (1) with Levulinic Acid

Levulinic acid (0.241 mL, 2.35 mmol) was slowly added to a stirred suspension of L-phenylalanine hydroxamic acid (**1a**) (0.326 g, 1.81 mmol) in toluene (30 mL) at 120 °C. After the reaction mixture was stirred for 2 h at the same temperature, it was carefully concentrated to about 10 mL by evaporation and stood at room temperature overnight. The precipitated white solid was filtrated and washed with diethyl ether to afford bicyclic hydroxamic acid **3a** (0.397 g, 84%). The stereochemistry of **3a** was determined by NOE experiments and X-ray diffraction analysis.

(3*S*,7a*R*)-3-Benzyl-1-hydroxy-7a-methyl-dihydro-1*H*-pyrrolo [1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (3a)

Colorless crystal; mp 205 °C; R_f 0.35 (ethyl acetate); $[\alpha]_D^{25} + 118$ (c = 1.0, $CHCl_3$); IR (KBr) 3127, 2928, 2867, 1727, 1700, 1666, 1458, 1332, 702, 574 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.99 (s, 3H), 2.17–2.45 (m, 3H), 2.61–2.76 (m, 1H), 3.07 (dd, $J = 5.9$, 13.9 Hz, 1H), 3.16 (dd, $J = 5.3$, 13.9 Hz, 1H), 4.60 (t, $J = 5.9$ Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 24.0, 30.9, 34.7, 36.9, 58.3, 82.3, 127.1, 128.5, 129.9, 135.9, 168.4, 178.6. Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.34; H, 6.17; N, 10.66.

Crystal Data for 3a

$C_{14}H_{16}N_2O_3$; M = 260.29, colorless block crystals, 0.30 × 0.30 × 0.10 mm, orthorhombic, space group P212121 (no. 19), $a = 11.327(7)$, $b = 13.653(6)$,

$c = 8.520(3)$ Å, $V = 1317.(1)$ Å^3, $Z = 4$, $Dc = 1.31$ g cm^{-3}. $F(000) = 552$, $\mu(CuK\alpha) = 0.769$ mm^{-1}.

Typical Experimental Procedure for the Cyclocondensation of Aromatic L-α-Aminohydroxamic Acids (1) with Levulinic Acid

Levulinic acid (**1d**) (0.241 mL, 2.35 mmol) was slowly added to a stirred suspension of L-tryptophan hydroxamic acid (0.397 g, 1.81 mmol) in 2-propanol (30 mL) at 80 °C. The mixture was stirred at the same temperature and monitored by thin-layer chromatography (TLC). After stirring for 2 h at 80 °C, the temperature was raised to 120 °C, and toluene (35 mL) was added in small portions to remove 2-propanol by azeotropic distillation. After an additional stirring for 7 h, the volatile compounds were evaporated under reduced pressure. Dichloromethane and Na_2CO_3 were added to the mixture and stirred vigorously for 1 h. The precipitated crystal was filtrated and washed with diethyl ether to give bicyclic hydroxamic acid **3d** (0.516 g, 95%).

(3*S*,7a*R*)-1-Hydroxy-3-(1*H*-indol-3-ylmethyl)-7a-methyl-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (3d)

Colorless crystal; mp 219–220 °C; R_f 0.34 (ethyl acetate); $[\alpha]_D^{25} + 74.7$ (c = 1.0, methanol); IR (KBr) 3311, 2658, 1698, 1509, 1459, 1427, 1354, 1136, 751, 595 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 0.65 (s, 3H), 2.07–2.34 (m, 3H), 2.61–2.70 (m, 1H), 3.21–3.37 (m, 2H), 4.52 (t, $J = 4.9$ Hz, 1H), 6.95–7.08 (m, 3H), 7.30 (d, $J = 8.1$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (68 MHz, CD_3OD) δ 23.5, 27.3, 31.9, 36.0, 59.7, 83.6, 110.8, 112.2, 119.6, 119.8, 122.4, 124.9, 129.6, 137.8, 170.1, 180.8. Anal. calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.79; H, 5.73; N, 13.95.

Cyclocondensation of L-Phenylalanine Hydroxamic Acid (1a) with *o*-Formylbenzoic Acid

L-Phenylalanine hydroxamic acid (**1a**) (0.360 g, 1.81 mmol), *o*-formylbenzoic acid (0.300 g, 2.00 mmol), *p*-toluenesulfonic acid monohydrate (0.038 g, 0.20 mmol), and benzene (20 mL) were refluxed in a 50-mL, two-necked flask equipped with Dean–Stark apparatus for 20 h, after which no more water appeared to be evolved from the reaction. The mixture was concentrated by evaporation until a white solid appeared. The solid was filtered off, and the filtrate stood at room temperature. The precipitated white solid was filtered and washed with ether to afford tricyclic hydroxamic acid **9** (0.421 g, 72%). The stereochemistry of **9** was determined by NOE experiments.[20]

(3*S*,9b*R*)-3-Benzyl-1-hydroxy-1,9b-dihydro-imidazo[2,1-*a*]isoindole-2(3*H*),5-dione (9)

Colorless crystal; mp 189–190 °C; R_f 0.51 (ethyl acetate); $[\alpha]_D^{25} + 153$ (c = 1.0, $CHCl_3$); IR (KBr) 3063, 2924, 2831, 1716, 1695, 1374, 1215, 742, 706, 695, 507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (dd, $J = 5.1$, 13.9 Hz, 1H), 3.21 (dd, $J = 4.1$,

13.9 Hz, 1H), 4.59 (t, $J = 4.4$ Hz, 1H), 4.79 (s, 3H), 7.22–7.35 (m, 5H), 7.53–7.63 (m, 3H), 7.81 (d, $J = 7.2$ Hz, 1H), 9.67 (br s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 37.1, 58.8, 74.7, 124.3, 124.8, 127.4, 128.6, 129.9, 130.7, 131.8, 133.2, 135.1, 142.1, 172.5, 173.5. Anal. calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.22; H, 4.79; N, 9.48.

SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENTS

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