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A Convenient Route to Enantiopure 3-Aryl-2,3-diaminopropanoic Acids by Diastereoselective Mannich Reaction of Camphor-Based Tricyclic Iminolactone with Imines

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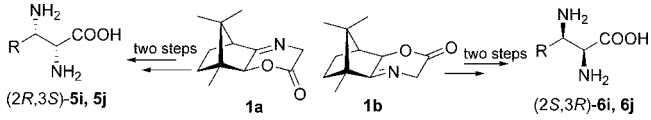

A novel and convenient route to the asymmetric synthesis of 2,3-diamino acids via Mannich reaction of iminolactones **1a** and **1b** with *N*-protected imines has been achieved in good yields (up to 95%) and high diastereoselectivity (dr: >99:1). Hydrolysis of the Mannich adducts under acidic conditions furnished the desired 3-aryl-2,3-diaminopropanoic acids in good yields (up to 85%) with excellent enantiomeric excesses (99% ee).

Optically active 2,3-diamino acids are an important class of compounds due to their presence in a variety of peptide antibiotics, antifungal dipeptides, and other biologically active compounds.[1] One example is (2*R*,3*S*)-2,3-diamino-3-phenylpropanoic acid, which is an alternative side chain of taxol to improve its water solubility.[2] As a consequence, a range of methods to synthesize optically active 2,3-diamino acid derivatives have been reported so far.[3] However, almost all of them suffer from one or more drawbacks including lack of generality, low-yielding, or complex procedures. Furthermore, to the best of our knowledge, there have been only a few reports for the synthesis of free 2,3-diamino acids.[3b,4] The Mannich reaction[5] was discovered in 1912 and is one of the most important carbon−carbon bond-forming reactions for the synthesis of nitrogenous molecules, such as diamino acid derivatives[6] and amino alcohols, which can lead to the generation of two contiguous nitrogen-bearing stereogenic centers. Thus, we report a novel and convenient approach to generate optically pure 2,3-diamino acids in high yields with excellent diastereoselectivity via asymmetric Mannich reaction of *N*-protected imines with zinc enolates of tricyclic iminolactones **1a** and **1b**[7] derived from natural (1*R*)-(+)-camphor.

Our investigation began with the reaction of iminolactone **1a** with various *N*-aryl-substituted imines, but no Mannich adducts were detected. Given the low reactivity of imines in this nucleophilic addition, a strong electron-withdrawing group, such as sulfonyl, was introduced on the nitrogen atom of the imine in order to activate the C=N bond. Fortunately, we found that *N*-tosyl-*C*-phenyl imine **2a** reacted smoothly with iminolactone **1a** at −78 °C in THF using LDA as the base to afford a mixture of diastereomeric adducts. The result suggested that the electron-withdrawing imine-protecting group played an important role in this nucleophilic addition. Thus, we chose the *N*-tosyl-*C*-phenyl imine **2a** as a substrate for further investigation.

In an attempt to improve the yield and the diastereoselectivity, we carried out a series of experiments varying the additives and bases used. Representative results are listed in Table 1. Commonly used additives, such as LiCl, DMPU, or Et_2AlCl, either failed to promote the reaction (entry 1) or gave the addition adducts in low yields with poor diastereo-

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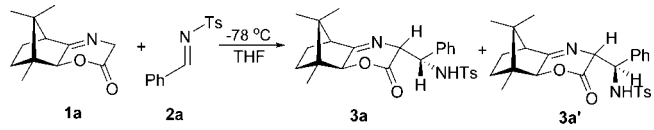
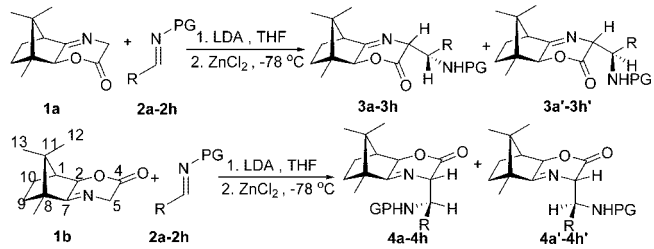
TABLE 1. Mannich Reaction of Iminolactone 1a with *N*-Tosyl-*C*-phenyl Imine 2a



entry	base (equiv)	additive (equiv)	dr[a]	yield (%)
1	LDA(1.2)	LiCl(6)	complex	
2	LDA(1.2)	DMPU(3)	100:37:26:13	58[b]
3	LDA(1.2)	Et_2AlCl(2.2)	100:67:24:0	32[b]
4	LDA(1.2)	$ZnCl_2$(1.2)	>99/1	91[c]
5	LHMDS(1.2)	$ZnCl_2$(1.2)	>99/1	91[c]
6	KHMDS(1.2)	$ZnCl_2$(1.2)	>99/1	90[c]

[a] The ratios were estimated by ^{1}H NMR integrations of the crude reaction mixtures. [b] Yield of the inseparable diastereomeric mixture after silica gel column chromatography. [c] Isolated yield.

TABLE 2. Mannich Reaction of Tricyclic Iminolactones 1a and 1b with *N*-tosyl Imines 2a-h



entry	substrate	PG	R	product	dr[a]	yield (%)[b]
1	**1a**	Ts	Ph	**3a**	>99:1	91
2	**1a**	Ts	*p*-CH_3Ph	**3b**	>99:1	94
3	**1a**	Ts	*o*-CH_3Ph	**3c**	>99:1	87
4	**1a**	Ts	*m*-CH_3Ph	**3d**	>99:1	86
5	**1a**	Ts	*p*-CH_3OPh	**3e**	>99:1	95
6	**1a**	Ts	*o*-CH_3OPh	**3f**	>99:1	91
7	**1a**	Ts	*p*-ClPh	**3g**	>99:1	93
8	**1a**	Ts	2-furyl	**3h**	>99:1	91
9	**1b**	Ts	Ph	**4a**	>99:1	95
10	**1b**	Ts	*p*-CH_3Ph	**4b**	>99:1	91
11	**1b**	Ts	*o*-CH_3Ph	**4c**	>99:1	82
12	**1b**	Ts	*m*-CH_3Ph	**4d**	>99:1	87
13	**1b**	Ts	*p*-CH_3OPh	**4e**	>99:1	85
14	**1b**	Ts	*o*-CH_3OPh	**4f**	>99:1	83
15	**1b**	Ts	*p*-ClPh	**4g**	>99:1	84
16	**1b**	Ts	2-furyl	**4h**	>99:1	92

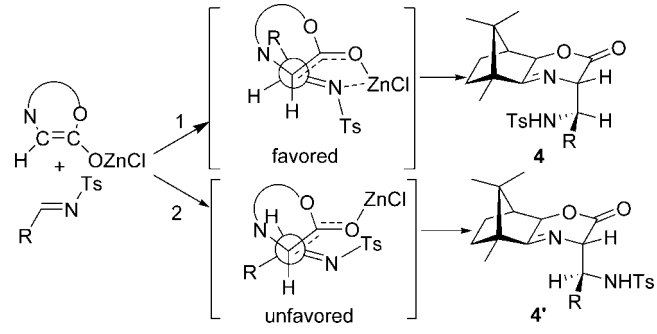
[a] The ratios were estimated by ^{1}H NMR integrations, we cannot find other isomers from crude reaction mixtures. [b] Yield of the major products after silica gel column chromatography.

selectivity (entries 2 and 3). However, addition of 1.2 equiv of zinc chloride ($ZnCl_2$)[8] dramatically improved both the yield (91%) and the diastereoselectivity (dr: >99:1) affording a complete conversion of the starting materials to the product **3a** as a single isomer in less than 30 min (entry 4). Other bases, such as lithium hexamethyldisilazide (LHMDS) and potassium hexamethyldisilazide (KHMDS), could also give the same results as LDA (entries 5 and 6).

Encouraged by these results, we next examined the scope of the reaction under the optimized conditions. Results obtained in the addition of tricyclic iminolactones **1a** and **1b** to a variety of *N*-tosyl imines **2a**−**h** are summarized in Table 2. All reactions were conducted in THF at −78 °C in the presence of $ZnCl_2$ with LDA as the base.

As revealed in Table 2, high yields (82–95%) and excellent diastereoselectivities (dr: >99:1) were obtained with all the substrates. The high diastereoselectivity, which is consistent with our previous results,[7] suggests that the Mannich reaction should take place from the *endo* face of the enolate to give the *endo*-isomer as the predominant product. The extremely high *endo*/*exo* ratio for the Mannich products is presumably due to the steric hindrance of C_{12}-methyl, which effectively blocks the reaction approach from the *exo*-face and thus favors the reaction of the electrophile from the *endo*-face of the enolate.

SCHEME 1. Proposed Mechanism of Mannich Reaction of 1b with Imines



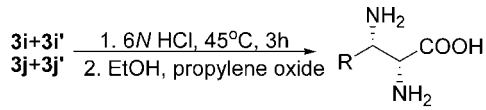
Although the NMR spectroscopic data support the formation of the Mannich adducts, the absolute and relative configurations

TABLE 3. Mannich Reaction of Tricyclic Iminolactones 1a and 1b with *N*-Boc Imines 2i−k

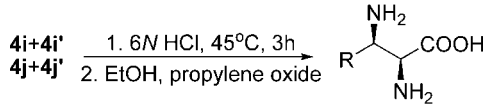
entry	substrate	PG	R	products	dr[a]	yield (%)[b]
1	**1a**	Boc	Ph	**3i**+ **3i′**	50:1	82
2	**1a**	Boc	*p*-CH_3Ph	**3j**+ **3j′**	33:1	81
3	**1a**	Boc	*m*-CH_3Ph	**3k**+**3k′**	30:1	71
4	**1b**	Boc	Ph	**4i**+ **4i′**	50:1	86
5	**1b**	Boc	*p*-CH_3Ph	**4j**+ **4j′**	22:1	81
6	**1b**	Boc	*m*-CH_3Ph	**4k**+**4k′**	20:1	79

[a] The ratios were estimated by ^{1}H NMR integrations after silica gel column chromatography. [b] Isolated yield of the two isomers.

TABLE 4. Hydrolysis of Mannich Products



(2*R*,3*S*)-**5i**,**5j**



(2*S*,3*R*)-**6i**,**6j**

entry	substrate	product	yield (%)	dr[a]	ee (%)[a]
1	**3i** + **3i′**	**5i**	78	95.1/4.9	>99
2	**3j** + **3j′**	**5j**	75	97.3/2.7	>99
3	**4i** + **4i′**	**6i**	85	96/4	>99
4	**4j** + **4j′**	**6j**	79	97/3	>99

[a] Determined by HPLC analysis on a CR(+) column.

were unambiguously confirmed through X-ray crystal structure analysis of compounds **3d** and **4c** (see the Supporting Information).[9]

The high diastereoselectivity led us to propose the mechanism to account for the stereochemical induction of the reaction. The zinc enolate of tricyclic iminolactone **1b** is formed in situ from the corresponding lithium enolate via transmetalation with 1 equiv of zinc chloride. As shown in Scheme 1, two possible pathways for the reaction are depicted. Obviously, the coordination of the imine via the lone pair of electrons on the nitrogen with the zinc center enables a six-membered cyclic transition state in pathway 1. This model can account for both the *endo* configuration and the high diastereoselectivity. By contrast, in pathway 2, the bulky sulfonyl group within the imine would not allow for efficient interaction with the zinc center.

Subsequently, we attempted to hydrolyze the Mannich adducts under acidic conditions, but the procedure has suffered from a few problems: (1) removal of the *p*-toluenesulfonate (tosyl) group was difficult under mild conditions[10] and (2) racemization could occur under acidic conditions and reducing the acidity or lowering the reaction temperature from 80 to 45 °C could not suppress the racemization. The best result was achieved in moderate diastereoselectivity (dr: 15:1) by treatment with 6 N HCl at 45 °C. In view of these problems, we turned our attention to *N*-Boc imines as an electrophile because of the fact that a Boc protecting group can be readily removed under acidic conditions.

Thus, a series of Mannich reactions with *N*-Boc imines **2i−k** were then conducted as summarized in Table 3. It is noteworthy that two diastereoisomers generated in the case of *N*-Boc imines cannot be separated and the diastereomeric ratios were estimated by ^{1}H NMR integrations. The predominant *endo* configurations were the same as those of *N*-tosyl imines. The structure was also assigned by X-ray crystallographic analysis of compound **3j** (see the Supporting Information).[9]

Facile deprotection of the *N*-Boc group and removal of the chiral auxiliary could be achieved under acidic conditions. It is exciting that the racemization was not detected and both 3-aryl-(2*S*,3*R*)-2,3-diaminopropanoic acids and 3-aryl-(2*R*,3*S*)-2,3-diaminopropanoic acids were obtained in very high diastereoselectivies with predominantly >99% ee (Table 4).

In conclusion, we have developed a simple and efficient method for the preparation of both free 3-aryl-(2*S*,3*R*)-2,3-diaminopropanoic acids and its enantiomers in high yield via Mannich reaction of *N*-protected imines with zinc chelated enolates derived from tricyclic iminolactones. Diastereo- and enantioselectivies obtained in this manner are very high compared with those obtained by previously reported methods. Detailed mechanistic studies of the reaction, especially to clarify the high diastereoselectivity, are ongoing.

Experimental Section

General Procedure for Mannich Reaction of Iminolactone and *N*-Protected Imines. Preparation of iminolactones **1a** and **1b** was described in ref 7. *N*-Tosyl imines **2a−h** and *N*-Boc imines **2i−k** were synthesized according to the reported procedure.[11,12]

Diisopropylamine (0.17 mL, 1.20 mmol) was added to dry THF (8.0 mL) in a long-neck flask under argon. After the solution was cooled to −78 °C, *n*-BuLi (2.163 M, 0.56 mL, 1.20 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min. Iminolactone (207 mg, 1.0 mmol) in dry THF (8.0 mL) was added to the above freshly prepared LDA solution at −78 °C and the solution was stirred for 20 min. Then a solution of anhydrous $ZnCl_2$ (163 mg, 1.2 mmol) in dry Et_2O (2.0 mL) was added and stirring was continued for 30 min followed by the addition of imine (1.2 mmol) in dry THF (5.0 mL), then the reaction mixture was stirred for another 30 min at −78 °C and saturated NH_4Cl solution (1.0 mL) was added to quench the reaction. The solvent was removed under reduced pressure and the residue was diluted with diethyl ether (3 × 15 mL). The resulting mixture was washed with water (3 × 3.0 mL) and brine (3 × 3.0 mL), dried over anhydrous $MgSO_4$, and then concentrated to give the crude product. The crude product was purified by flash column chromatography to yield the desired compound.

(1*S*,2*R*,5*S*,8*R*,1′*R*)-5-(1′-*p*-Tolylsulfinylaminobenzyl)-8,11,11-trimethyl-3-oxa-6-azatricyclo[6.2.1.0^{2,7}]undec-6-en-4-one (4a). 4a was purified by chromatography (EtOAc/petroleum = 1/5) as a white solid: yield 95%; $[\alpha]^{26}_D$ −15 (*c* 1.0, CH_2Cl_2); mp 140–142 °C; IR (KBr) 2960, 1733, 1334, 1161, 703, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.63 (d, J = 8.0 Hz, 2H), 7.29–7.26 (m, 1H), 7.22–7.15 (m, 4H), 7.03 (d, J = 8.8 Hz, 2H), 6.21 (d, J = 8.4 Hz, 1H), 4.84 (dd, J = 8.4, 4.4 Hz, 1H), 4.70 (d, J = 4.4 Hz, 1H), 2.36 (s, 3H), 2.19 (s, 1H), 1.81 (d, J = 4.8 Hz, 1H), 1.78–1.71 (m, 1H), 1.60–1.53 (m, 1H), 1.30–1.23 (m, 1H), 0.99 (s, 3H), 0.81 (s, 3H), 0.65 (s, 3H), 0.60–0.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 183.6, 170.2, 143.3, 137.5, 136.5, 129.4, 128.5, 128.4, 127.4,

(8) It is very important to use dry $ZnCl_2$, otherwise the yields and diastereoselectivity will be lower. Therefore, $ZnCl_2$ was dried with a heat gun under vacuum.

(9) Crystal data for **3d**, **3j**, and **4c** have been deposited in CCDC as deposition numbers 672090, 672091, and 672092, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.com.

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126.9, 79.2, 65.4, 57.5, 52.9, 48.3, 47.0, 28.6, 25.8, 21.4, 19.8, 19.3, 10.0; HRMS (calcd for $C_{26}H_{31}N_2O_4S$) 467.1999, found 467.1995 ($M + H^+$).

General Procedure for Hydrolysis of Mannich Products. The Mannich product (80 mg) was dissolved in 6 N HCl (3 mL) in a sealed tube with a Teflon screw cap and heated at 45 °C for 3 h. After it was cooled to room temperature, water (5 mL) was added and the mixture was extracted with diethyl ether (3 × 5 mL). The separated aqueous layer was evaporated under reduced pressure and the residue was dissolved in EtOH (5 mL). Propylene oxide (2 mL) was then added to the above solution and the mixture was stirred at room temperature for 30 min. The white solid started to precipitate, which was collected by filtration under reduced pressure and washed with cold EtOH (2 × 2 mL) and Et_2O (1 × 4 mL) to give the desired 2,3-diamino acid.

3-Phenyl-(2*S*,3*R*)-2,3-diaminopropanoic acid (6i). 6i was obtained as a white solid: yield 85%; $[\alpha]^{26}_D$ +39 (*c* 0.52, H_2O); mp 189–191 °C; IR (KBr) 3419, 2920, 1650, 1531, 768, 703 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ (ppm) 7.54–7.49 (m, 5H), 4.65 (d, J = 11.2 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ (ppm) 171.0, 131.5, 131.1, 130.3, 128.1, 54.6, 54.4; HRMS (calcd for $C_9H_{13}N_2O_2$) 181.0972, found 181.0972 ($M + H^+$). Diastereomeric ratio 96/4, enantiomeric excess >99%, determined by HPLC.

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Supporting Information Available: Crystallographic data for products **3d**, **4c**, and **3j** (CIF), copies of ^1H and ^{13}C NMR spectra, characterization data for all new compounds, and HPLC results. This material is available free of charge via the Internet at http://pubs.acs.org.

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