Synthesis of Marine Alkaloids Isonaamine A, Dorimidazole A, and Preclathridine A. Iminophosphorane-Mediated Preparation of 2-Amino-1,4-disubstituted Imidazoles from α-Azido Esters

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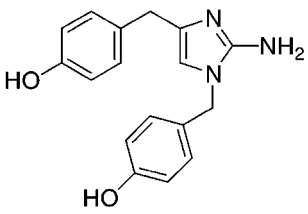
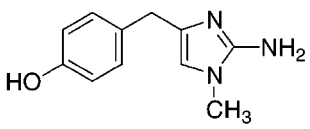
The preparation of 2-amino-1,4-disubstituted imidazoles from α-azido esters is described. The aza-Wittig reaction of the iminophosphorane derivatives with tosyl isocyanate followed by treatment with primary amines afforded the appropriately substituted 2-aminoimidazolinone ring. Reduction with DIBAL, dehydration with methanesulfonyl chloride, and further *N*-tosyl deprotection provided the target molecules. A highly facile and practical synthesis of the marine alkaloids isonaamine A, dorimidazole A, and preclathridine A is outlined.

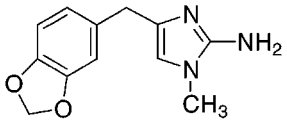
Marine organisms are among the most promising sources of new biologically active molecules. Certain secondary metabolites are nontraditional guanidine-based alkaloids[1] that possess a broad spectrum of powerful biological activities. The guanidine moiety is most frequently found in the guise of a 2-aminoimidazole ring that embodies one or two benzyl-substituted moieties.[2] Examples include isonaamine A[3] (**1**), isolated from the calcareous Red Sea sponge *Leucetta chagosensis*, dorimidazole A[4] (**2**), and preclathridine A[5] (**3**), isolated from the Indo-Pacific nudibranch *Notodoris gardineri*.



Isonaamine A **1**



Dorimidazole A **2**



Preclathridine A **3**

A survey of the literature reveals that classical methods for the preparation of 2-aminoimidazole derivatives involve condensation of α-aminocarbonyl compounds with cyanamide,[6] reaction of α-diketones with guanidine followed by reduction,[7] and reaction of α-haloketones with *N*-acetylguanidine.[2i] Only three methods, starting from a preformed imidazole ring, allow the direct introduction of the amino functionality at position 2: coupling with arene diazonium salts and further reduction,[8] metalation followed by sequential treatment with aryl azide and acid,[9] and oxidation of a sulfur substituent at position 2 with *tert*-butylhydroperoxide and further treatment with ammonia.[10]

In connection with the synthesis of a number of imidazole-containing alkaloids from marine origin,[11] we have reported three iminophosphorane-mediated methods that provide convenient entries to functionalized imidazole derivatives.[12] However, these methods do not allow the introduction of a suitable amino functionality at position 2 of the imidazole ring.

We now report an efficient iminophosphorane-based approach that has sufficient flexibility to allow 2-amino-1,4-disubstituted imidazoles to be conveniently generated from a variety of ethyl 3-aryl propionates and its suitable use for the preparation of the alkaloids **1**−**3**, demonstrating the application of this chemistry. The key step, formation of the appropriate substituted imidazole ring, involves a Staudinger/aza-Wittig/carbodiimide-mediated cyclization process.

Our strategy to synthesize 2-amino-1,4-disubstituted imidazoles **11** is illustrated in Scheme 1. The α-azido ester **4a** was prepared in 60% yield from the ethyl 3-phenylpropionic ester by the enolate azidation procedure described by Evans[13] using LDA/2,4,6-triisopropylbenzenesulfonyl azide[14] (trisyl azide)/HMPA. One-flask conversion of the α-azido ester **4a** into the appropriately

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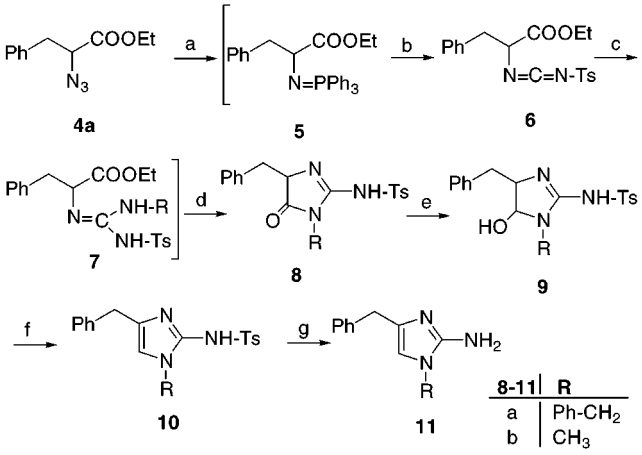
Scheme 1



Reagents and conditions: (a) PPh_3 / Et_2O, rt; (b) Ts-NCO, Et_2O, rt; (c) R-NH_2, Et_2O, 0°C; (d) Et_2O, rt; (e) DIBAL, THF, reflux; (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2, rt; (g) SmI_2, THF, reflux.

substituted imidazolones **8** was achieved in 60% yield by sequential treatment with triphenylphosphine, tosyl isocyanate, and the adequate primary amine (methyl or benzylamine) at room temperature. The conversion **4a** → **8** involves an initial Staudinger reaction between the α-azido ester **4a** and triphenylphosphine to give the iminophosphorane **5**, which was used without purification for the next step. Compound **5** reacts in aza-Wittig-type fashion with tosyl isocyanate to afford the carbodiimide **6** (as evidenced by the appearance of a strong band at 2129 cm^{-1} in the IR spectrum). Reaction of the carbodiimide **6** with primary amines leads to a guanidine-substituted intermediate **7**, which under the reaction conditions undergoes regioselective imidazole ring formation across the ester and alkylamino functionality to give **8**. The choice of the tosylisocyanate in the conversion **5** → **8** is derived from its demonstrated reactivity in aza-Wittig reactions not only to give carbodiimides in high yields but also to promote the regioselective cyclization of the guanidine **7** across the more nucleophilic alkylamino group. The next task was to effect the reduction of the carbonyl group of the imidazolone **8**. After several trials with various reagents that included $NaBH_4/TiCl_4$; $NaBH_4$/*t*-BuOH; $BH_3{\cdot}SMe_2$; H_2/Pd/C; $LiAlH_4/Et_2O$; and $NaBH_4/CH_3-SO_3H$/DMSO, we were unable to accomplish this transformation. This series of frustrating results was finally broken by using of DIBAL. Thus, treatment of imidazolone **8a** (R = $PhCH_2$) with DIBAL in THF at reflux temperature provided the hydroxyimidazole derivative **9a** (R = $PhCH_2$) as a single diastereoisomer in 67% yield, which was easily converted into the N-protected imidazole **10a** (R = $PhCH_2$) in 98% yield by the action of methanesulfonyl chloride in the presence of triethylamine. In the ^1H NMR spectrum of compound **9a**, the observed coupling constant between H-4 and H-5 (J = 6.5 Hz) suggests that the OH substituent on C-5 is equatorial. However, reduction of imidazolone **8b** (R = Me) under the same conditions provided a mixture of the expected hydroxyimidazole **9b** (R = Me) and 4-benzyl-1-methyl-2-tosylamino-4,5-dihydroimidazole. All attempts to separate these compounds by column chromatography were unsuccessful. However, when this mixture was submitted to the above dehydration conditions, the imidazole **10b** (R = CH_3) was obtained in 45% yield after chromatographic separation.[15]

Removal of the *N*-tosyl protecting group, essential to our objective of preparing naturally ocurring 2-aminoimidazole derivatives, proved to be difficult. Application to **10** of the reaction conditions shown to achieve complete deprotection of *N*-(arylsulfonyl) amines (TBAF/THF,[16] refluxing in HBr,[17] and sodium naphthalenide[18]) led to the product decomposition. Finally, on the basis of the reaction conditions used to remove *N*-sulfonyl protecting groups using samarium diiodide,[19] complete deprotection of **10** to give **11** was achieved by the action of an excess of samarium diiodide in THF in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). After 4 h, complete deprotection of **10** was observed by TLC, and the products, compounds **11a** and **11b**, were isolated in 95−90% yields, respectively (Scheme 1).

With these exploratory results in hand, the 4-methoxybenzyl derivative **4b** was then employed for the preparation of isonaamine A (**1**), one of our primary goals in applying iminophosphorane methodology to naturally occurring 2-aminoimidazoles. Azidation of ethyl 3-(4-methoxyphenyl)propionate under the Evans conditions provided the α-azido ester **4b** in 58% yield. Direct conversion of compound **4b** into the imidazolone derivative **8c** was achieved in 57% yield by sequential treatment with triphenylphosphine, tosylisocyanate, and O-MOM-protected 4-hydroxybenzylamine. Reduction of compound **8c** with DIBAL (1:4 molar ratio) afforded a mixture of the hydroxyimidazole **9c** (50% yield) and the corresponding 4,5-dihydroimidazole (26% yield). However, when a 1:3 molar ratio was used, the desired compound **9c** was obtained as the sole product in 76% yield. Dehydration of the hydroxyimidazole **9c** with methanesulfonyl chloride led to **10c** in 98% yield. Conversion of the imidazolone **8c** into the imidazole **10c** can also be achieved in the same yield without the isolation of the intermediate hydroxyimidazole **9c** by sequential treatment of **8c** with DIBAL and methanesulfonyl chloride. Deprotection of the two phenolic groups with boron tribromide gave **12** in 95% yield, whereas the *N*-sulfonyl deprotection with samarium diiodide provided the 2-aminoimidazole **13** in 98% yield. Attempt to convert **13** into the target molecule **1** by deprotection of the two phenolic groups with boron tribromide failed, and only a complex mixture was obtained. However, *N*-tosyl deprotection of

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(15) During the chromatographic separation of compound **10b**, the 4-benzyl-1-methyl-2-tosylamino-4,5-dihydroimidazole could be isolated as a crystalline solid (mp 97−100 °C) in 30% yield.

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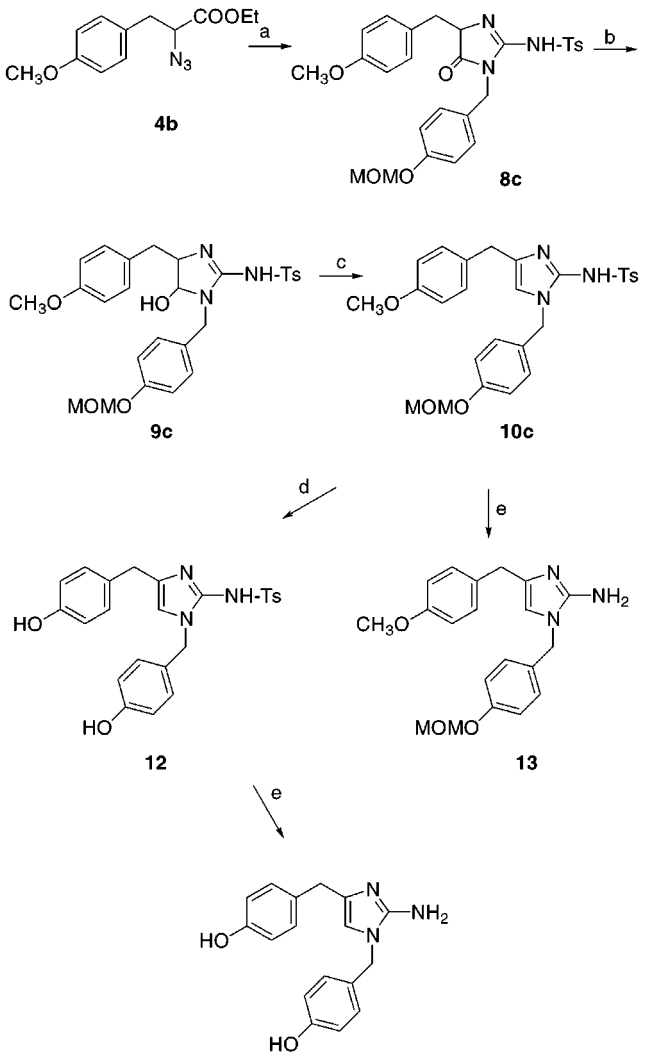
Scheme 2. Synthesis of Isonaamine A

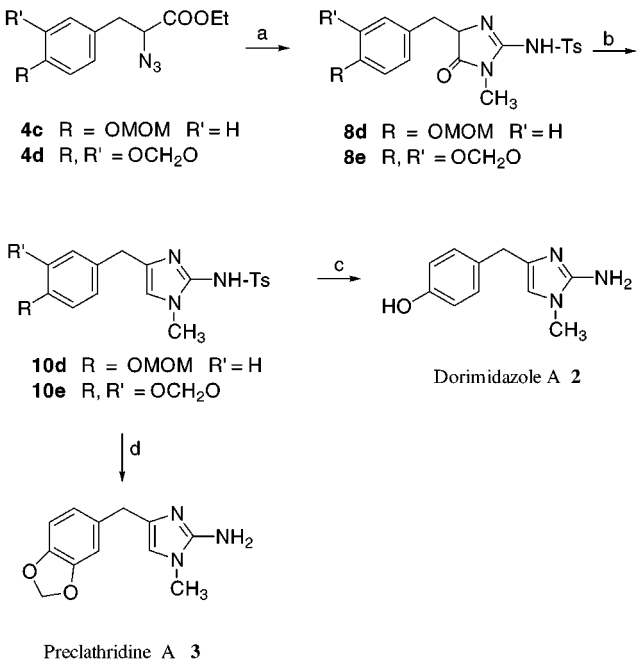


Reagents and conditions: (a) i: PPh_3 , Et_2O, rt; ii: Ts-NCO, Et_2O, rt; iii:4-$MOMOC_6H_4CH_2NH_2$, Et_2O, rt; (b) DIBAL, THF, reflux; (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, rt; (d) BBr_3, CH_2Cl_2, reflux; (e) SmI_2, THF, reflux.

compound **12** with samarium diiodide provided **1** in 76% yield (Scheme 2).

In a similar way, the synthesis of dorimidazole A (**2**) was achieved starting from the α-azido ester **4c**, readily available from 3-(4-hydroxyphenyl)propionic acid in a three-step sequence consisting of (a) esterification (91%), (b) O-MOM protection of the phenolic group (87%), and (c) azidation with trisyl azide (51%). Formation of the imidazolone derivative **8d** was achieved in 50% yield from **4c** by sequential treatment with triphenylphosphine, tosylisocyanate, and methylamine. When compound **8d** was submitted to reduction with DIBAL and further treatment with methanesulfonyl chloride/triethylamine, the imidazole derivative **10d** was isolated in 42% yield along with the corresponding O-MOM-protected 4-(4-hydroxybenzyl)-1-methyl-2-tosylamino-4,5-dihydroimidazole (31%). Direct conversion of the imidazole derivative **10d** into **2** was achieved in 76% by sequential treatment with samarium diiodide (N-deprotection) and HCl (O-deprotection) (Scheme 3).

Scheme 3. Synthesis of Dorimidazole A and Preclathridine A



Reagents and conditions:
(a) i: PPh_3 , Et_2O, rt; ii: Ts-NCO, Et_2O, rt; iii: $MeNH_2$, Et_2O, rt.
(b) i: DIBAL, THF, reflux; ii: $MeSO_2Cl$, Et_3N, CH_2Cl_2, rt.
(c) i:SmI_2, THF, reflux; ii: 6N HCl, THF, rt.
(d) SmI_2, THF, reflux.

Finally, α-azido ester **4d**, available in 52% yield by azidation of the ethyl 3-(3,4-methylendioxyphenyl)propionate, was converted into the imidazolone **8e** in 60% yield by the same protocol used for the preparation of **8d**. Compound **8e** by sequential treatment with DIBAL and methanesulfonyl chloride produced the imidazole derivative **10e** as the sole reaction product in 67% overall yield. *N*-Tosyl deprotection using samarium diiodide provided preclathridine A (**3**) in 65% yield. (Scheme 3). Spectroscopic data of the synthetic compounds **1**−**3** are in good agreement with those previously reported for the compounds of natural origin (see Experimental Section).

The preparation of 2-amino-1,4-disubstituted imidazoles from α-azido esters is described. The method appears to be general and its utility is demonstrated in the synthesis of the marine alkaloids isonaamine A, dorimidazole A, and preclathridine A. The key step centered around a cyclization strategy of a novel guanidine precursor to create the appropriately substituted imidazole ring. Although explicit here, this process should have additional applications to a variety of marine alkaloids containing the 2-aminoimidazolin-4-one (discapamide), 2-amino-4-substituted imidazole (oroidin), or 2-amino-1,4,5-trisubstituted imidazole ring (naamine A).

Experimental Section

General Methods. General experimental conditions and spectroscopic instrumentation used have been described.[20]

Materials. The 3-arylpropionic esters were prepared by standard chemistry. Ethyl 3-(4-methoxyphenyl)propionate was

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prepared in 94% yield by esterification[21] of the commercially available carboxylic acid. Ethyl 3-(4-methoxymethylenoxyphenyl) propionate was prepared from 3-(4-hydroxyphenyl)propionic acid by esterification[21] (91%) and further O-MOM protection with methoxymethyl chloride in the presence of sodium hydride[22] (87%). Ethyl 3-(3,4-methylendioxyphenyl)propionate was prepared in 54% yield from ethyl 3-(3,4-dihydroxyphenyl)propionate by reaction with bromodichloromethane in the presence of cesium carbonate.[23] The O-MOM-protected 4-hydroxybenzylamine was prepared from 4-hydroxybenzaldehyde by a three-step sequence consisting of (a) O-MOM protection with methoxymethyl chloride in the presence of sodium hydride[22] (98%), (b) formation of the corresponding aldoxime (88%), and (c) catalytic hydrogenation in the presence of Pd on charcoal[24] (50%).

α-Azido Esters (4a−d). General Procedure. To a solution of diisopropylamine (1.06 g, 69.8 mmol) in anhydrous tetrahydrofuran (150 mL) was added dropwise *n*-butyllithium (1.6 M, 41 mL, 67.2 mmol). The solution was stirred at −78 °C under dry N_2 for 45 min. A solution of the appropriate ethyl 3-arylpropionate (11.2 mmol) in anhydrous tetrahydrofuran (40 mL) was added dropwise. The resultant solution was warmed to −30 °C, stirred at that temperature for 1 h, and then recooled to −78 °C. Hexamethylphosphoric triamide (HMPA) (30.5 mL, 175.5 mmol) was added in one portion, and to the above enolate solution was added a precooled (−78 °C) solution of trisyl azide (13.84 g, 44.8 mmol) in anhydrous tetrahydrofuran (80 mL). The reaction mixture was stirred at −78 °C for 1 h and then was quenched with glacial acetic acid (14.8 mL, 256 mmol). The resulting mixture was allowed to warm to room temperature, stirred for 12 h, treated with a saturated solution of $NaHCO_3$ (300 mL), and extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, washed with a NaCl solution (1 × 100 mL) and water (2 × 100 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on a silica gel column using dichloromethane/*n*-hexane (4:3 v/v) as eluent to give **4a**−**d**.

Ethyl 2-Azido-3-phenylpropionate (4a): 60% yield; colorless oil; IR (film) 1743, 2117 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.3 Hz), 3.0 (dd, 1H, J = 14.0, 8.6 Hz), 3.17 (dd, 1H, J = 14.0, 5.6 Hz), 4.04 (dd, 1H, J = 8.6, 5.6 Hz), 4.21 (q, 2H, J = 7.3 Hz), 7.1−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 37.5, 61.8, 63.1, 127.1, 128.3, 128.6, 135.9, 169.8; EIMS *m*/*z* 219 (M^+, 1), 191 (1), 176 (9), 91 (100). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H,5.98; N, 19.17. Found: C, 60.40; H, 6.14; N, 19.28.

2-Tosylamino-1,4-disubstituted Imidazolones (8a−e). General Procedure. To a 0 °C solution of triphenylphosphine (0.447 g, 1.7 mmol) in dry ether (10 mL) was added dropwise a solution of the appropriate α-azido ester **4** (1.7 mmol) in the same solvent (10 mL) under N_2. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. To the recooled (0 °C) solution was added a solution of tosylisocyanate (0.335 g, 1.7 mmol) in dry ether (10 mL) under N_2. The mixture was allowed to warm to room temperature, stirred for 1 h, and then recooled to 0 °C. A solution of the appropriate primary amine (1.7 mmol) in dry ether (10 mL) was added, and the resulting mixture was allowed to warm to room temperature and stirred for 12 h. The solution was concentrated to dryness, and the solid residue was chromatographed on a silica gel column using ethyl acetate/dichloromethane (1:4 v/v) as eluent to give **8a**−**e**.

1,4-Dibenzyl-4*H*-2-tosylaminoimidazol-5-one (8a): 60% yield; white prism, mp 148−150 °C (ethyl acetate/*n*-hexane); IR (Nujol) 1632, 1764, 2308 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.04 (dd, 1H, J = 14.1, 5.7 Hz), 3.18 (dd, 1H, J = 14.1, 4.5 Hz), 4.39 (dd, 1H, J = 5.7, 4,5 Hz), 4.50 (d, 1H, J = 14.4 Hz), 4.61 (d, 1H, J = 14.4 Hz), 6.93 (d, 2H, J = 8.1 Hz), 7.0−7.22 (m, 10H), 7.55 (d, 2H, J = 8.1 Hz), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 36.8, 42.7, 59.0, 126.1, 127.4, 127.6, 128.2, 128.3, 128.7, 129.2, 129.4, 133.5, 134.8, 139.0, 142.8, 156.4, 171.8; EIMS *m*/*z* 434 (M^+ + 1, 2), 433 (M^+, 8), 278 (24), 155 (13). Anal. Calcd for $C_{24}H_{23}N_3O_3S$: C, 66.49; H, 5.35; N, 9.69. Found: C, 66.63; H, 5.19; N, 9.82.

2-Tosylamino-5-hydroxy-1,4-disubstituted-4,5-dihydroimidazoles (9a and 9c). General Procedure. A 20% hexane solution of DIBAL (2.9 mL, 2.86 mmol) was added dropwise at room temperature under N_2 to a solution of imidazolone **8a** or **8c** (0.95 mmol) in freshly distilled tetrahydrofuran (35 mL). The reaction mixture was heated at reflux for 5 h. After the mixture cooled, the excess of hydride was destroyed by careful addition of 0.1 N HCl (20 mL). After 5 min of stirring, a 5% solution of NaOH was added until pH = 8. The mixture was extracted with ethyl acetate (3 × 20 mL) and dried ($MgSO_4$). After evaporation of the solvent, the residual solid was triturated with ether and recrystallized from the appropriate solvent or chromatographed to give **9a** or **9c**.

1,4-Dibenzyl-5-hydroxy-2-tosylamino-4,5-dihydroimidazole (9a): 67% yield; white needle, mp 153−154 °C (ethyl acetate/*n*-hexane); IR (Nujol) 1607, 3298, 3321 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.85 (dd, 1H, J = 13.7, 8.6 Hz), 3.02 (dd, 1H, J = 13.7, 6.1 Hz), 3.88 (ddd, 1H, J = 8.6, 6.5, 6.1 Hz), 4.21 (d, 1H, J = 15.2 Hz), 4.87 (d, 1H, J = 15.2 Hz), 4.95 (d, 1H, J = 6.5 Hz), 6.95 (s, 1H), 7.10−7.30 (m, 13H), 7.72 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 34.4, 44.4, 59.3, 80.2, 126.1, 127.4, 127.6, 128.2, 128.6, 128.9, 129.0, 129.2, 136.3, 137.0, 140.3, 142.2, 156.9; EIMS *m*/*z* 417 ($M^+ - H_2O$, 69), 328 (19), 262 (100), 155 (28). Anal. Calcd for $C_{24}H_{25}N_3O_3S$: C, 66.19; H, 5.79; N, 9.65. Found: C, 66.33; H, 5.62; N, 9.49.

5-Hydroxy-4-(4-methoxybenzyl)-1-(4-methoxymethylenoxy)benzyl-2- tosylamino-4,5-dihydroimidazole (9c): silica gel, ethyl acetate/dichloromethane (1:4 v/v); 76% yield; mp 169−170 °C (ethyl acetate/*n*-hexane); IR (Nujol) 1511, 1585, 3395 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.78 (dd, 1H, J = 14.0, 8.7 Hz), 2.95 (dd, 1H, J = 14.0, 6.0 Hz), 3.43 (s, 3H), 3.74 (s, 3H), 3.81 (m, 1H), 4.13 (d, 1H, J = 15.1 Hz), 4.08−4.27 (brs, 1H), 4.78 (d, 1H, J = 15.1 Hz), 4.95 (d, 1H, J = 6.5 Hz), 5.10 (s, 2H), 6.80 (d, 2H, J = 8.4 Hz), 6.86 (d, 2H, J = 8.4 Hz), 6.91 (s, 1H), 7.04−7.12 (m, 4H), 7.22 (d, 2H, J = 8.1 Hz), 7.71 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3, 33.5, 43.7, 55.2, 55.9, 59.4, 80.0, 94.31, 114.2, 116.2, 126.0, 128.9, 129.1, 129.6, 129.9, 140.4, 142.1, 156.5, 156.7, 158.5; EIMS *m*/*z* 507 ($M^+ - H_2O$, 41), 401 (29), 352 (14) 214 (100), 151 (43), 121 (52). Anal. Calcd for $C_{27}H_{31}N_3O_6S$: C, 61.70; H, 5.94; N, 7.99. Found: C, 61.83; H, 5.78; N, 8.14.

2-Tosylamino-1,4-disubstituted Imidazoles (10). Method A. To a mixture of 2-tosylamino-5-hydroxy-4,5-dihydroimidazole **9a** or **9c** (1.1 mmol), methanesulfonyl chloride (0.11 mL, 1.4 mmol), and anhydrous dichloromethane (30 mL) was added dropwise triethylamine (0.46 mL, 3.3 mmol) at 0 °C under N_2. The resultant mixture was stirred at room temperature for 12 h. Dichloromethane (70 mL) and saturated solution of NaCl (30 mL) were added. The organic layer was dried ($MgSO_4$) and concentrated to dryness. The residual solid was triturated with ether and recrystallized from the appropriate solvent to give **10a** or **10c**. **Method B.** A 20% hexane solution of DIBAL (5.97 mL, 5.88 mmol) was added dropwise at room temperature to a solution of the appropriate imidazolone **8b**, **8d**, or **8e** (1.96 mmol) in anhydrous tetrahydrofuran (80 mL). The mixture was heated at reflux temperature for 5 h. After the mixture cooled, the solution was poured with stirring into cold 0.1 N HCl (20 mL), and 5% solution of NaOH was added until pH = 8. The mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with H_2O (2 × 20 mL) and dried ($MgSO_4$). After filtration, the solvent was removed, and the residue was dissolved in anhydrous dichloromethane (50 mL). To this solution were added methanesulfonyl chloride (0.2 mL, 2.53 mmol) and triethylamine (0.81 mL, 5.81 mmol) at 0 °C under N_2. The resultant mixture was stirred at room temperature for 12 h. Workup was the same as that described for method A. After removal of the solvent, the residue was applied to a column of silica gel and eluted with ethyl acetate/dichloromethane (1:4 v/v). The appropriate fractions were collected and evaporated to give pure **10b**, **10d**, and **10e**.

1,4-Dibenzyl-2-tosylaminoimidazole (10a): 98% yield; mp 179−180 °C (ethyl acetate/*n*-hexane); IR (Nujol) 1567, 3340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.74 (s, 2H), 4.84 (s, 2H), 5.95 (s, 1H), 7.0−7.35 (m, 12H), 7.71 (d, 2H, J = 8.2 Hz), 10.05 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 31.3, 47.9, 110.5, 124.9, 125.7,

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127.1, 127.8, 128.0, 128.5, 128.7, 128.8, 129.0, 135.4, 135.9, 141.3, 141.5, 147.0; EIMS *m*/*z* 417 (M^+, 100), 328 (61), 262 (61), 155 (56). Anal. Calcd for $C_{24}H_{23}N_3O_2S$: C, 69.04; H, 5.55; N, 10.06. Found: C, 69.27; H, 5.39; N, 10.29.

1,4-Bis(4-hydroxybenzyl)-2-tosylaminoimidazole (12). To a solution of compound **10c** (0.2 g, 0.4 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise at room temperature a solution of BBr_3 (0.54 g, 2.12 mmol) in the same solvent (4 mL). The mixture was heated at reflux for 30 min. After the mixture cooled, MeOH (4 mL) was added. The resultant solution was concentrated to dryness. The residue was dissolved in THF (12 mL) and 6 N HCl (12 mL) was added. The mixture was stirred at room temperature for 12 h. Then, a saturated solution of $NaHCO_3$ was added until pH = 6, and the mixture was extracted with AcOEt (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was recrystallized from AcOEt/*n*-hexane (1:1 v/v) to give **12**: 95% yield; mp 200−202 °C (ethyl acetate); IR (Nujol) 1241, 1385, 1583, 3288 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.34 (s, 3H), 3.65 (s, 2H), 4.68 (s, 2H), 6.39 (s, 1H), 6.63 (d, 2H, J = 8.0 Hz), 6.69 (d, 2H, J = 8.2 Hz), 6.95 (d, 2H, J = 8.0 Hz), 6.98 (d, 2H, J = 8.2 Hz), 7.23 (d, 2H, J = 7.8), 7.67 (d, 2H, J = 7.8 Hz), 8.6−9.9 (brs, 2H, OH), 11.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.9, 29.5, 46.5, 111.2, 115.2, 115.17, 125.5, 126.1, 126.8, 128.1, 129.5, 129.2, 129.4, 140.8, 142.0, 145.3, 155.9, 156.9; EIMS *m*/*z* 450 ($M^+ + 1$, 12), 449 (M^+, 16), 343 (88), 188 (100), 107 (85), 91 (85). Anal. Calcd for $C_{24}H_{23}N_3O_4S$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.27; H, 5.03; N, 9.57.

2-Amino-1,4-disubstituted Imidazoles (11 and 13). General Procedure. Samarium power (0.75 g, 5 mmol) was placed in a reaction flask fitted with a dropping funnel. A solution of 1,2-diiodoethane (0.7 g, 2.5 mmol) in anhydrous and deoxygenated THF (30 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, and then a mixture of the appropriate compound **10** (0.24 mmol), DMPU (2.54 g, 2.4 mmol), and anhydrous and deoxygenated THF (5 mL) was added. The resultant solution was heated at reflux temperature for 4 h. After the mixture cooled, a 5% solution of NaOH (10 mL) was added, and the mixture was stirred for 30 min. The solvent was removed under reduced pressure, and the residue was extracted with AcOEt (2 × 25 mL) and $CHCl_3$/MeOH (4:1 v/v) (1 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to dryness. The residue was washed with *n*-hexane (3 × 25 mL) and then chromatographed on a silica gel column using $CHCl_3$/MeOH (4:1 v/v) as eluent to give **11** and **13**.

1,4-Dibenzyl-2-aminoimidazole (11a): 95% yield; yellow viscous oil; IR ($CHCl_3$) 1665, 3140, 3309 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 2H), 5.04 (s, 2H), 4.90 (brs, 2H), 6.06 (s, 1H), 7.15−7.45 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 32.2, 48.6, 111.4, 126.5, 127.4, 128.1, 128.4, 128.6, 128.8, 129.9, 134.7, 137.2, 147.4; EIMS *m*/*z* 264 ($M^+ + 1$, 19), 263 (M^+, 67), 172 (46), 91 (100). Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.66; H, 6.38; N, 15.77.

4-Benzyl-1-methyl-2-aminoimidazole (11b): 90% yield; yellow viscous oil; IR (Nujol) 3113, 3245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.48 (s, 3H), 3.73 (s, 2H), 6.07 (s, 1H), 6.89 (brs, 2H), 7.2−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 31.0, 33.6, 113.1, 126.8, 127.0, 128.6, 128.7, 135.8, 146.4; EIMS *m*/*z* 188 ($M^+ + 1$, 36), 187 (M^+, 100), 172 (49). Anal. Calcd for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.64; H, 7.23; N, 22.63.

4-(4-Methoxybenzyl)-1-(4-methoxymethylenoxy)benzyl-2-aminoimidazole (13): 98% yield; yellow viscous oil; IR ($CHCl_3$) 1660, 3134, 3303 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.37 (s, 3H), 3.73 (s, 5H), 5.02 (s, 2H), 5.20 (s, 2H), 6.71 (s, 1H), 6.90 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.64 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 29.1, 46.9, 55.1, 55.5, 93.7, 112.5, 113.9, 116.3, 126.4, 128.3, 129.1, 129.2, 129.5, 145.8, 155.9, 156.5; EIMS *m*/*z* 354 ($M^+ + 1$, 31), 353 (M^+, 100), 309 (69), 247 (62), 202 (80). Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.75; H, 6.34; N, 11.72.

Isonaamine A (1). Starting from **12** and using the above-described procedure, isonaamine A was obtained in 76% yield as a yellow viscous oil: IR (Nujol) 1518, 1662, 3247 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.63 (s, 2H), 4.89 (s, 2H), 6.57 (s, 1H), 6.70 (d, 2H, J = 8.6 Hz), 6.76 (d, 2H, J = 8.6 Hz), 7.02 (d, 2H, J = 8.5), 7.14 (d, 2H, J = 8.6 Hz), 7.43 (s, 2H), 9.0−9.8 (brs, 2H); ^{13}C NMR (DMSO-d_6) δ 29.5, 40.1, 112.2, 115.3, 116.5, 125.6, 127.2, 127.6, 129.3 (2C), 129.5 (2C), 146.0, 156.1, 157.3; EIMS *m*/*z* 295 (M^+, 48), 200 (28), 189 (100), 188 (60), 128 (92), 127 (46), 107 (35), 96 (37), 77 (16); HREIMS $C_{17}H_{17}N_3O_2$ calcd 295.1321, found 295.1303.

Dorimidazole A (2). Starting from **10d** and using the same procedure followed by treatment with 6 N HCl in THF at room temperature, dorimidazole A was obtained in 76% yield as a viscous oil: IR (Nujol) 1161, 1380, 1460, 1568, 1602, 1686, 3258 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.39 (s, 3H), 3.66 (s, 2H), 6.61 (s, 1H), 6.72 (d, 2H, J = 8.5 Hz), 7.04 (d, 2H, J = 8.5 Hz), 7.43 (s, 2H), 9.31 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.3, 32.0, 113.9, 115.3, 126.0, 127.5, 129.6 (2C), 146.3, 156.2; FABMS (positive) *m*/*z* 205 (M + 2, 19), 204 (M + 1, 100), 203 (M^+, 21); HREIMS $C_{11}H_{13}N_3O$ calcd 203.1058, found 203.1047.

Preclathridine A (3). This compound was prepared in 65% yield as a yellow viscous oil from **10e** using the same *N*-tosyl deprotection procedure: IR (film) 756, 927, 1037, 1245, 1490, 1663, 3147, 3286 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.57 (s, 3H), 3.72 (s, 2H), 5.92 (s, 2H), 6.17 (s, 1H), 6.68−6.76 (m, 3H), 6.80−7.8 (brs, 2H); ^{13}C NMR ($CDCl_3$) δ 30.6, 33.8, 101.0, 108.0, 109.0, 113.0, 121.8, 126.6, 129.2, 146.3, 146.5, 147.7; EIMS *m*/*z* 232 ($M^+ + 1$, 14), 231 (M^+, 100), 216 (32), 175 (12), 135 (4), 127 (23); HREIMS $C_{12}H_{13}N_3O_2$ calcd 231.1008, found 231.0983.

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Supporting Information Available: Spectroscopic data (IR, NMR, MS) for α-azido esters **4b**−**d**, 2-tosylaminoimidazol-5-ones **8b**−**e**, and 2-tosylaminoimidazoles **10b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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