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Full Papers

Selective Hydrolysis of Ethyl 5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carboxylate and Ethyl 5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazole-3-carboxylate as a Key Step in the Large-Scale Synthesis of Bicyclic Heteroaryl Carboxyaldehydes

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Abstract:

The isomeric mixture of ethyl 5,6-dihydro-4H-pyrrolo[1,2-*b*]-pyrazole-2- and −3-carboxylates (14 and 15), derived from a proline meso-ionic synthon, demonstrated remarkably different stabilities towards alkaline hydrolysis. On that basis, a non-chromatographic, highly efficient method for their large-scale separation was developed. The desired isomer 14 was converted into 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carbaldehyde, a key intermediate in the synthesis of bicyclic heteroaryl-substituted 6-alkylidene penems.

Introduction

New, improved antibiotics continue to be in demand for the treatment of human infectious diseases. According to the World Health Organization, more than 95% of the *Staphylococcus aurei* isolated worldwide are now resistant to penicillin, and up to 60% are resistant to methicillin.[1] Resistance is spreading from hospital-acquired infections to community-acquired pathogens, such as *Pneumococci* and *Mycobacterium* tuberculosis.

Penicillins and cephalosporins are the most frequently and widely used β-lactam antibiotics. However, the development of resistance to β-lactam antibiotics by different pathogens has had a damaging effect on maintaining the effective treatment of bacterial infections.[2] The most significant known mechanism to the development of bacterial resistance is the degradation of the β-lactam moiety by class-A, class-B, and class-C serine β-lactamases, resulting in the loss of antibacterial activity. Class-A enzymes preferentially hydrolyze penicillins, whereas class-C lactamases have a substrate profile favoring cephalosporin hydrolysis.[3] To date, there are over 250 known β-lactamases,[4] and there is a need for new generation of broad-spectrum β-lactamase inhibitors.

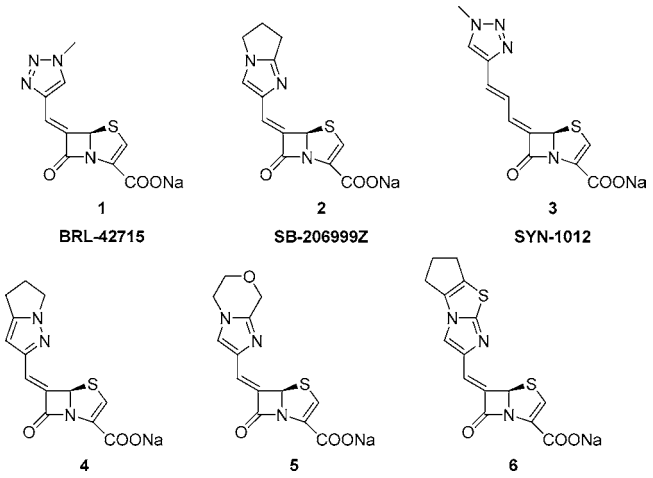

Figure 1. **Beecham compounds (1−3) and Wyeth bicyclic (4,5) and tricyclic (6) 6-methylidene penem derivatives.**

It was shown by Beecham chemists that 6-alkylidene-penems such as **1**−**3** (Figure 1) are broad-spectrum β-lactamase inhibitors.[5a] Recently, we disclosed a number of 6-methylidene penem derivatives, **4**−**6** (Figure 1), bearing heterobicyclic and heterotricyclic substituents that were shown to be broad-spectrum β-lactamase inhibitors.[5b−d] Among them, (5*R*,6*Z*)-6-(5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazol-2-yl-methylene)-7-oxo-4-thiazabicyclo[3.2.0]hept-2-ene-2-carboxylic acid sodium salt, **4**, became a target for large-scale synthesis.

Previously, we devised a novel method to synthesize this class of molecules by a two-step sequence: (a) aldol addition and (b) reductive elimination (Scheme 1).[6a,b] In this procedure, the appropriately substituted aldehydes were reacted

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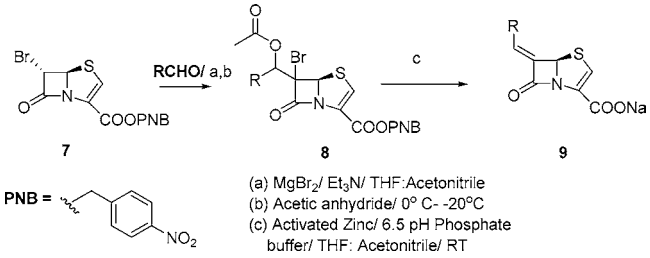
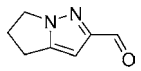
Scheme 1. **General method to prepare 6-methylidene penem derivatives**



with (5*R*,6*S*)-6-bromo-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboylic acid 4-nitrobenzyl ester, **7**, in the presence of triethylamine and anhydrous $MgBr_2$ or a similar Lewis acid. The aldol product was acetylated to form compound **8**. The double bond formation at the 6-position and the deprotection of the carboxylic acid were accomplished in a single step by reacting intermediate **8** with activated Zn in a pH 6.5 phosphate-buffered solution. To accomplish our goal of the large-scale synthesis of the target compound **4**, we needed the key intermediate 5,6-dihydro-4H-pyrrolo[1,2-*b*]-pyrazole-2-carbaldehyde, **10** (Figure 2), in large quantity.



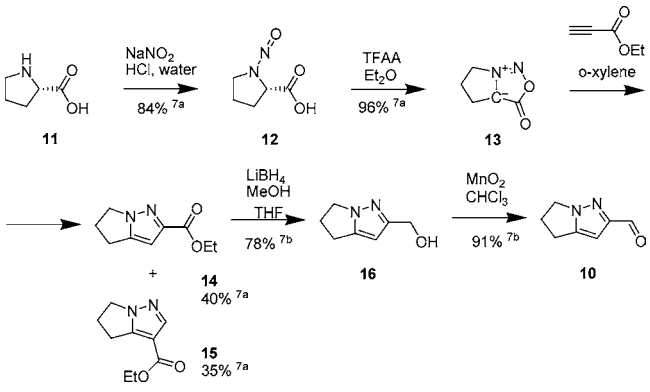
10

Figure 2. **5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carbaldehyde, the key intermediate for the synthesis of lead candidate 4.**

Results and Discussion

Initially we prepared aldehyde **10** from commercially available L-proline, **11** (Scheme 2).[7a−c] The first three steps were done as described by Ranganathan et al.:[7a] proline was nitrosated to provide **12** and subsequently converted to sydnone derivative **13**. Reaction of **13** with ethyl propiolate in boiling *o*-xylene produced a mixture of isomeric 5,6-dihydro-4H-pyrrolo-[1,2-*b*]pyrazole-2- and -3-carboxylates, **14** and **15**, in an approximately 1:1 ratio. The mixture was separated on a silica gel column (we used heptane/ethyl acetate instead of benzene/ethyl acetate), and desired isomer **14** was converted into target aldehyde **10** through intermediate alcohol **16**.[7b,c]

Scheme 2. **Synthesis of compound 10 by the literature route**



This sequence of reactions posed several scale-up problems. The first reaction, the nitrosation, proceeded well. The product was isolated by extraction with methyl *tert*-butyl ether (MTBE), followed by the azeotropic drying of the resulting crude product with toluene. Conversion of nitrosoproline **12** to sydnone **13** by reaction with trifluoroacetic anhydride in diethyl ether was very problematic—it did not give us the described 96% yield. Instead, the yield was in the range of 68−70%. Diethyl ether was not acceptable for scale-up, and the purification of the product required chromatography on silica gel to remove the generated trifluoroacetic acid. Also, as sydnone **13** is water soluble, aqueous workup had to be avoided or minimized to reduce the loss of the sydnone in an extractive procedure. We had to find an alternative solvent and neutralization procedure. After many experiments, we found that performing the reaction in acetonitrile resulted in complete conversion within 2 h. The neutralization was performed with powdered potassium carbonate. The resulting mixture was concentrated to dryness, producing a glasslike substance, which was thoroughly suspended in methylene chloride. The methylene chloride suspension was filtered to remove the residual potassium carbonate and potassium trifluoroacetate. This procedure enabled us to isolate sydnone **13** in 91% yield as a crystalline, low-melting solid; NMR analysis did not show any significant byproducts. Although this process was adequate for medium-scale work, it was not satisfactory for a kilogram-scale process. After further optimization, the conditions for the synthesis of the sydnone were modified as follows: The reaction between L-nitrosoproline (after azeotropic drying) and trifluoroacetic anhydride was performed in toluene, and the trifluoroacetic acid generated was neutralized using a concentrated aqueous solution of potassium carbonate. The sydnone, **13**, was extracted with dichloromethane, and the combined organic extracts were evaporated azeotropically to remove residual water. The sydnone, **13**, was isolated as a dark-colored, low-melting solid in an overall yield of 60−80% from L-proline. These reaction conditions were carried out successfully on a 2.5-kg scale.

As we progressed from gram-scale to kilogram-scale procedures, we performed safety evaluations of intermediates **12**, **13**, **14**, and **15** in the thermal screening unit (TSU). According to the results, nitrosoproline **12** has a decomposition exotherm at 68 °C; sydnone **13** has a significant decomposition exotherm at 180 °C. Isomers **14** and **15** were tested on TSU as a mixture, and no major exotherm or residual pressure was detected. All operations with intermediates **12** and **13** were therefore performed below the decomposition temperatures by at least 30 °C. We carried out all solvent evaporations under vacuum with a bath temperature at or below 35 °C. We were also aware that for

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multikilogram scale it would be necessary to develop an alternative approach to the target compound.

The next step, the 1,3-dipolar cycloaddition of ethyl propiolate to sydnone **13**, resulted in a mixture of isomeric esters **14** and **15.** Huisgen and Gotthard have studied the general reaction and reported the predominance of the 3-carboxylate regioisomer.[8] This particular reaction was described in detail, including the reaction mechanism, by Rangavanath et al., who obtained isomers **14** and **15** in 40:35 ratio after 8 h of reflux in xylene.[7a] We observed a similar result when the reaction was carried out in *o*-xylene. To improve the reaction conditions and increase the ratio of the desired isomer, we screened a number of other solvents including mesitylene, *N*,*N*-dimethylformamide (DMF), 1,2-dimethoxymethane, 1,2-diethoxyethane, and chlorobenzene at various temperatures. The best product ratio of 2.2:1 in favor of the desired isomer, **14**, was achieved in DMF at 120 °C. However, the reaction was slow (16 h) and was accompanied by the noticeable formation of a polymeric side product. Performing the cycloaddition in 1,2-diethoxyethane was superior for a combination of reasons: the reaction was faster (8 h at 120−125 °C) and cleaner (no polymer formation). Consequently, although the final ratio of **14**:**15** was slightly inferior to that in DMF, approximately 1.5:1, the isolated yield of target ester **14** was ultimately better.

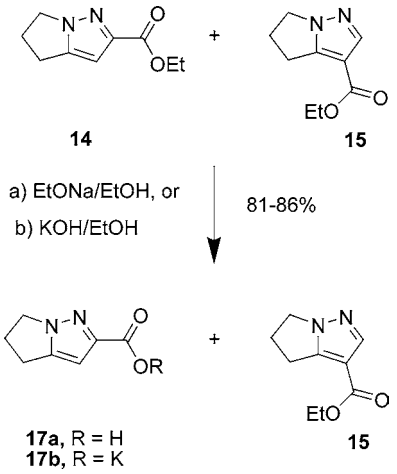
None of these conditions, however, addressed the major problem of this step, the chromatographic separation of esters **14** and **15**. Column chromatography is never desired in large-scale synthesis, and this particular mixture was especially difficult to separate. The esters **14** and **15** had very close retention times and different UV-absorption characteristics (the undesired isomer **15** is adequately visible only at 215 nm). We definitely needed an alternative to chromatographic separation.

We considered selective hydrolysis of the mixture of esters to facilitate their separation. The first idea was enzymatic hydrolysis; the selectivity difference in enzymatic hydrolyses of carboxylic esters in position 3 vs 5 on a pyrazole ring has been reported by Conte et al.[9] While this possibility was being evaluated by the Bioprocess Development Group, we examined selective chemical hydrolysis. Our rationale was that isomer **14** is potentially more reactive to hydrolysis due to both steric and electronic factors. The ester functionality in compound **15** is more sterically hindered than that of **14** (because of the $-CH_2-$ group at the peri position). Furthermore, we expected the ester functionality in compound **14** to be more reactive towards nucleophilic attack than the equivalent functional group in compound **15** because of the adjacent nitrogen atom.

Thus, the mixture of esters was stirred in 3A ethanol with one equivalent of sodium ethoxide overnight at room temperature. HPLC analysis showed that a single ester was left with the other completely hydrolyzed. The two products were easily separated by acid/base extraction.

Analysis of the isolated products indicated that, as predicted, the undesired ester **15** had remained unchanged, while the target isomeric ester, **14**, was hydrolyzed into the acid, **17a** (Scheme 3). The remarkable success of this procedure provided us with a simple, efficient, and scalable procedure to separate the two isomeric esters without chromatography. Further optimization of the selective hydrolysis step resulted in a procedure that used potassium hydroxide in ethanol and allowed isolation of the target acid by simple filtration of its crystalline potassium salt, **17b**. This selective hydrolysis reaction was carried out on a scale of 1−3 kg to provide the potassium salt, **17b**, in isolated yields of 81−86%.

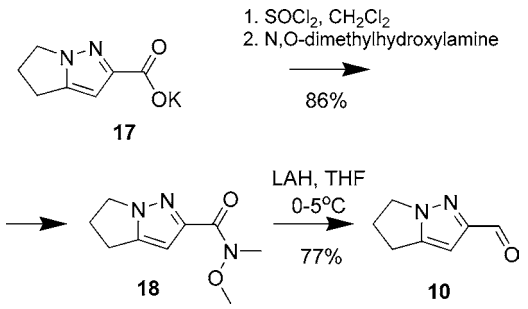
Scheme 3. **Selective hydrolysis of the desired isomer**



Interestingly, enzymatic hydrolysis led to the same result observed in the alkaline hydrolysis. When the mixture of esters was incubated with hydrolytic enzymes, ester **14** was converted into acid **17**, while ester **15** remained intact.[10]

Subsequently, the potassium salt, **17b**, was converted directly, without acid liberation or further purification, to the acid chloride. Reaction of the acid chloride with *N*,*O*-dimethylhydroxylamine gave Weinreb amide **18** (Scheme 4) in 85% yield. Reduction of the Weinreb amide, **18**, with lithium aluminum hydride provided the target aldehyde, **10** (Scheme 4), in 77% isolated yield. A similar transformation has been described in the work of Lee et al.[11]

Scheme 4. **Synthesis of 10 via Weinreb amide**



In conclusion, we report herein a remarkable difference in susceptibility of the two isomeric esters, **14** and **15**, towards alkaline hydrolysis that allowed us to avoid a chromatographic separation and develop a scalable process

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for synthesis of 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carbaldehyde **10**, the key intermediate in the synthesis of bicyclic heteroaryl substituted 6-alikylidene penem **4**.

Experimental Section:

General Methods. NMR spectra of the intermediates were recorded on a Bruker 300 NMR spectrometer. Structure elucidation for the target compound **10** was done on a Bruker Avance DPX 400 NMR spectrometer equipped with a 5 mm QNP 1H/13C/31P/19F Z-GRD probe. Spectra were referenced by an internal standard.

HPLC analysis of the intermediates and reaction monitoring was carried out on an Agilent 1090 liquid chromatograph equipped with a Phenomenex Prodigy ODS3 4.6 mm × 50 mm column. Standard method: 90:10 to 10:90 over 8 min gradient of water/acetonitrile containing 0.02% TFA, flow rate 1 mL/min.

Thermal screening tests were performed on the unit made by Hazard Evaluation Lan, Inc.

(2*S*)-1-Nitrosoproline 12. To a solution of L-proline (2.50 kg, 21.6 mol) and sodium nitrite (2.10 kg, 30.4 mol) in water (5.0 L) maintained at 0−10 °C was added concentrated hydrochloric acid (2.53 L), and the resulting slurry was stirred for 16 h at ambient temperature. The reaction mixture was extracted with *tert*-butyl methyl ether (6 L + 2 × 3 L), and the organic solution was concentrated using a rotary evaporator with a bath temperature below 35 °C. Residual water was removed by evaporation with 2.0 L of toluene. The resulting (2*S*)-1-nitrosoproline (3.25 kg, 105%) was isolated as a yellow solid and dried under vacuum at 25 °C, mp: 100−102 °C (lit.[7a] 106−107 °C, lit.[12] 100−101 °C); HPLC purity: 96.3% (215 nm, area %), and residual toluene: 4%. The product, (2*S*)-1-nitrosoproline **12**, was used directly, without further purification, in the next step.

3a,4,5,6-Tetrahydro-3-oxo-3H-pyrrolo[1,2-*c*][1,2,3]-oxadiazol-7-ium Ylide 13. Trifluoroacetic anhydride (3.86 kg, 18.4 mol) was added slowly to a suspension of (2*S*)-1-nitrosoproline **12** (1.75 kg, 12.2 mol from example 1) in toluene (6 L) below 10 °C. The resulting dark-red solution was stirred for 2 h at ambient temperature, and the reaction was quenched by adding the dark-red solution to a stirred mixture of potassium carbonate (2.70 kg, 19.6 mol), dichloromethane (3.5 L), and water (2.0 L) below 25 °C. Following complete addition and the subsequent separation of the upper organic layer, the aqueous layer was extracted with dichloromethane (3 × 3 L). The combined organic extracts were concentrated in vacuo using a rotary evaporator with a bath temperature not exceeding 35 °C. Residual water was removed by evaporation with toluene (2 L) to afford the title compound as a dark liquid, which solidified upon standing (917 g, 58% yield over two steps). The isolated product, 3a,4,5,6-tetrahydro-3-oxo-3H-pyrrolo[1,2-*c*][1,2,3]oxadiazol-7-ium ylide, **13**, was 89.8% pure by HPLC (area %) and 92.9% (potency); mp 33−38 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 2.75−2.83 (m, 2H), 2.90 (t, 2H, J = 7.1 Hz), 4.43 (t, 2H, J = 7.4 Hz); MS 127.1 (M + H). The product was used directly in the next step.

Ethyl 5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carboxylate, 14, and Ethyl 5,6-dihydro-4H-pyrrolo[1,2-*b*]-pyrazole-3-carboxylate, 15. 3a,4,5,6-Tetrahydro-3-oxo-3H-pyrrolo[1,2-*c*][1,2,3] oxadiazol-7-ium ylide, **13** (971 g, 7.70 mol, WAY-187725, made as in example 2) and 1,2-diethoxyethane (DEE, 2.9 L) were charged to a multinecked, 12-L round-bottomed flask, equipped with a water-cooled condenser. The stirred solution was purged with nitrogen and heated to 120−125 °C. Ethyl propiolate (971 g, 9.90 mol) was added dropwise over a period of 3 h (carbon dioxide evolution). The reaction was held at 120−125 °C for 5 h until the conversion was >99% (<1% of residual 3a,4,5,6-tetrahydro-3-oxo-3H-pyrrolo[1,2-*c*][1,2,3]oxadiazol-7-ium ylide **13** by GC−MS analysis). The mixture was then concentrated to a residue in vacuo using a rotary evaporator with a bath temperature up to 70 °C. About 1.5 kg of toluene was then added to the residue, and the mixture was concentrated once more. A dark oil was obtained (1218 g, 46.9% potency by HPLC, 41% yield, corrected for potency, of ethyl 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carboxylate, **14**, from crude 3a,4,5,6-tetrahydro-3-oxo-3H-pyrrolo[1,2-*c*][1,2,3]-oxadiazol-7-ium ylide, **13**). The individual esters were isolated on a silica gel column, using hexanes/ethyl acetate, 9:1 to 1:1 gradient, detection by HPLC, 215 nm. Compound **14**: mp 61−63 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 1.26 (t, 3H, J = 7.1 Hz), 2.54 (m, 2H), 2.85 (t, 2H, J = 7.4 Hz), 4.13 (t, 2H, J = 7.4 Hz), 4.23 (dd, 2H, J_1 = 7.4 Hz, J_2 = 7.1 Hz), 6.465 (s, 1H). Compound **15**: mp 40−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 1.33 (t, 3H, J = 7.3 Hz), 2.65 (m, 2H), 3.08 (t, 2H, J = 7.3 Hz), 4.16 (t, 2H, J = 7.3 Hz), 4.27 (dd, 2H, J_1 = 7.3 Hz, J_2 = 7.3 Hz), 7.899 (s, 1H).

Potassium 5,6-Dihydro-4H-pyrrolo-[1,2-*b*]pyrazole-2-carboxylate, 17. A freshly prepared solution of potassium hydroxide (87.6% w/w pellets, 307.6 g, 4.80 mol) in 2B-3 ethanol (absolute, 1.86 L) was added over a period of 1 h to a stirred solution of 1063.6 g [46.5% potency (HPLC), 2.744 mol] of the ester mixture, ethyl 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carboxylate, **14**, and ethyl 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-3-carboxylate, **15**, in 2B ethanol (absolute, 1.28 L) under a nitrogen atmosphere, while maintaining the temperature in the range 15−22 °C. The mixture was stirred for 4−7 h until ethyl 5,6-dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carboxylate, **14**, was consumed, as determined by HPLC. The slurry was filtered, and the filter cake was washed with 2B ethanol (1.8−2.4 L, in portions). The wet cake was dried under vacuum at 60−65 °C to constant weight. Crude potassium 5,6-dihydro-4H-pyrrolo-[1,2-*b*]pyrazole-2-carboxylate, **17**, 426.3 g, 81% (based on the calculated quantity of **14**) was obtained as a tan hygroscopic solid; ^{1}H NMR (300 MHz, DMSO-d_6, TFA) 2.51−2.58 (m, 2H), 2.85 (t, 2H, J = 7.3 Hz), 4.12 (t, 2H, J = 7.3 Hz), 6.43 (s, 1H). The cake may optionally be reslurried in 2B ethanol, if necessary, to remove impurities (such as potassium 5,6-dihydro-4H-pyrrolo-[1,2-*b*]pyrazole-

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(12) Lijinsky, W.; Keffer, L.; Loo, J. *Tetrahedron* **1970**, 5137.

3-carboxylate). The product was used directly in the next step.

***N*-Methoxy-*N*-methyl-5,6-dihydro-4H-pyrrolo[1,2-*b*]-pyrazole-2-carboxamide, 18.** To a stirred, cold (10−15 °C) slurry of crude potassium 5,6-dihydro-4H-pyrrolo-[1,2-*b*]-pyrazole- 2-carboxylate, **17** (123.6 g, 0.65 mol), in methylene chloride (1234 mL) containing *N*,*N*-dimethylformamide (1.8 g) under a nitrogen atmosphere in a 3-L multinecked, round-bottomed flask, fitted with a water cooled condenser, was added thionyl chloride (116.0 g, 0.97 mol) over a period of 45 min, while maintaining the temperature below 28 °C. The mixture was stirred for 1 h and monitored by HPLC until the conversion to the acid chloride was >97%. In a separate multinecked, 5-L round-bottomed flask, solid potassium carbonate (296.3 g, 2.14 mol) and *N*,*O*-dimethylhydroxylamine hydrochloride (95.0 g, 0.97 mol) were dissolved in water (1.2 L) and cooled to 10−15 °C. The acid chloride mixture was added to the separately prepared aqueous solution over a period of 45 min, while maintaining the temperature at about 10−20 °C. The biphasic mixture was stirred for about 1 h and then checked for completion by HPLC. The mixture was transferred to a separatory funnel, and the lower organic layer was separated. The organic layer was washed with water (1.2 L) and concentrated to a residue in vacuo using a rotary evaporator at 90 °C. Upon cooling, the residue, *N*-methoxy-*N*-methyl-5,6-dihydro-4H-pyrrolo-[1,2-*b*]-pyrazole-2-carboxamide, **18** (126.8 g, >99%), was obtained as a tan crystalline solid: mp 56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 2.58−2.65 (m, 2H), 2.91 (t, 2H, J = 7.2 Hz), 3.44 (s, 3H), 3.76 (s, 3H), 4.18 (t, 2H, J = 7.2 Hz), 6.49 (s, 1H); MS 196.1 (M + H). The tan crystalline solid amide **18** was used directly in the next step.

5,6-Dihydro-4H-pyrrolo[1,2-*b*]pyrazole-2-carbaldehyde 10. To a stirred, cold (0−5 °C) solution of *N*-methoxy-*N*-methyl-5,6-dihydro-4H-pyrrolo-[1,2-*b*]pyrazole-2-carboxamide, **18** (300 g, 1.54 mol), in anhydrous tetrahydrofuran (3 L) under a nitrogen atmosphere was added lithium aluminum hydride (pellets, 30 g, 0.79 mol) in portions over a period of 0.5 h. After stirring for 5 h at 0−5 °C the reaction was quenched by slowly adding saturated sodium sulfate solution (75 mL) to the stirred reaction mixture maintained at 5−15 °C. Magnesium sulfate (70 g) was added, and the mixture was stirred for 15 min. The mixture was then filtered, and the filter pad was washed with THF (1 L). The solvent was removed by evaporation at 20−70 °C under reduced pressure to provide a tan oil. The oil was diluted with dichloromethane (1 L), and the solution was washed with 1.5 N hydrochloric acid (350 mL). The organic layer was separated and concentrated in vacuo at 20−70 °C to an oil. Fresh dichloromethane (1 L) and water (1.5 L) containing dissolved sodium hydrogen sulfite (220 g) were added to the oil. The mixture was stirred for 15 min, and the phases were separated. The aqueous phase was washed with dichloromethane (2 × 300 mL). Dichloromethane (1 L) and 10 N sodium hydroxide (220 mL) were added (with cooling) to the aqueous phase, and the mixture was stirred for 10 min. The lower organic phase was separated and washed with water (500 mL). The dichloromethane extracts were combined and evaporated under reduced pressure at 20−70 °C to give an oil, which crystallized on cooling to provide 140.1 g (67%) of 5,6-dihydro-4H-pyrrolo-[1,2-*b*]pyrazole-2-carbaldehyde, **10**, as a white crystalline solid, mp 40−42 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 2.67−2.75 (m, 2H), 2.95 (t, 2H, J = 7.3 Hz), 4.22 (t, 2H, J = 7.3 Hz), 6.52 (s, 1H), 9.89 (s, 1H); MS 137.1 (M + H); HPLC−MS purity, 99.86%. Lit.:[7b] ^{1}H NMR ($CDCl_3$) 2.63−2.71 (m, 2H), 2.95 (t, 2H, J = 7.4 Hz), 4.22 (t, 2H, J = 7.4 Hz), 6.52 (s, 1H), 9.89 (s, 1H).

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