**N-Methylimidazole Promotes the Reaction of Homophthalic Anhydride with Imines**

Jian Liu,† Zheng Wang,† Aaron Levin,† Thomas J. Emge,† Paul R. Rablen,‡ David M. Floyd,† and Spencer Knapp*,†

†Department of Chemistry & Chemical Biology, Rutgers The State University of New Jersey, 610 Taylor Road, Piscataway, New Jersey 08854, United States
‡Department of Chemistry and Biochemistry, Swarthmore College, Swarthmore, Pennsylvania 19081, United States

*Supporting Information

**ABSTRACT:** The addition of N-methylimidazole (NMI) to the reaction of homophthalic anhydride with imines such as pyridine-3-carboxaldehyde-N-trifluoroethylimine (9) reduces the amount of elimination byproduct and improves the yield of the formal cycloadduct, tetrahydroisoquinolonic carboxylate 10. Carboxanilides of such compounds are of interest as potential antimalarial agents. A mechanism that rationalizes the role of NMI is proposed, and a gram-scale procedure for the synthesis and resolution of 10 is also described.

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**INTRODUCTION**

Malaria persists as a global health risk, with roughly 200 million cases of the disease reported in 2012, accompanied by an estimated 627,000 deaths.1 Antimalarial drugs remain among the most effective tools for defeating the Plasmodium agent, and new treatments are continually required as resistance to more traditional drugs such as artemisinin sets in.2 Phenotypic screening has proven to be a good source of lead compounds for this purpose, and a recent campaign examining more than 300,000 compounds for activity against *P. falciparum* in human erythrocytes revealed among the actives a series of tetrahydroisoquinolonic carboxanilides related to 1.3 Hit-to-lead studies have further identified carboxanilides 2 and 3 as worthy of further development. We have undertaken an investigation of methods to improve existing syntheses of this class of compounds and can report that N-methylimidazole has proven beneficial as a promoter of the formal cycloaddition reaction of homophthalic anhydride with aldimines.

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**RESULTS AND DISCUSSION**

A variety of methods have been described for the synthesis of 1-oxo-2-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids 8 by formal cycloaddition of homophthalic anhydride (HPA) 4 with aldimines 5 (Scheme 1).4 The reaction is commonly thought to proceed by way of a Mannich intermediate 6, the amino group of which subsequently closes upon the anhydride carbonyl group in a Perkin-analogous process leading to lactam acid 8.5 Alternatively, a more direct cycloaddition pathway leading to intermediate 7 or its tautomer has been considered.6 The reaction often goes well without additives or catalysts, but various improvements have been recommended.4,6,7 In our specific case with the N-2,2,2-trifluoroethylimine derived from pyridine-3-carboxaldehyde (i.e., 9, Table 1), the

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reaction under several literature conditions led to large amounts of an elimination pathway (see 12, Scheme 2) and associated downstream educts and other byproducts, accompanied by only modest yields of desired product 10. Aldimines of basic heterocyclic carboxaldehydes were generally troublesome as cycladdition partners. We, therefore, set about screening solvents and additives, including various weak bases and acyl transfer promoters, as displayed in Table 1.

By examining the crude reaction products by proton NMR spectroscopy in the presence of a known amount of an internal spectroscopy in the presence of a known amount of an internal

| base (equiv) | pK_a | solvent | NMR yield (trans/cis) |
|-------------|------|---------|----------------------|
| no base     |      | CHCl_3  | 47% (2.2:1)          |
| pyridine (1.0) | 5.2  | CHCl_3  | 45% (1:1)            |
| DABCO (1.0)  | 8.8  | CHCl_3  | b                   |
| 2,4,6-collidine (1.0) | 7.6 | CHCl_3  | b                   |
| N,N-diethylamine (1.0) | 6.6 | CHCl_3  | b                   |
| N-methylmorpholine (1.0) | 7.4 | CHCl_3  | b                   |
| 4-(dimethylamino)pyridine (1.0) | 9.2 | CHCl_3  | b                   |
| 4-(dimethylamino)pyridine (1.0) | 9.2 | CHCl_3  | b                   |
| 4-(4-morpholino)pyridine (1.0) | 8.0 | CHCl_3  | b                   |
| 4(1-pyrrolidino)pyridine (1.0) | 9.6 | CHCl_3  | b                   |
| HOAc (1.0)   | 4.8  | toluene | b                   |
| N-methylimidazole, NMI (1.0) | 7.0 | CHCl_3  | b                   |
| NMI (1.5)    |      | CHCl_3  | 68%                 |
| NMI (0.5)    |      | CHCl_3  | 65%                 |
| NMI (2.0)    |      | CHCl_3  | 78%                 |
| NMI (5.0)    |      | CHCl_3  | 53%                 |
| NMI (neat)   |      | CHCl_3  | b                   |
| NMI (1.0)    |      | CHCl_3  | b                   |
| NMI (1.0)    |      | CHCl_3  | 66%                 |
| NMI (1.0)    |      | 14 other solvents | b                   |

"Approximate pK_a of conjugate acid. \(^b\)Poor yield and/or messy reaction mixture. \(^\text{Solvents tried: methyl acetate, ethyl acetate, isopropyl acetate, isobutyl acetate, n-butyl acetate, ethyl lactate, dimethyl carbonate, diethyl carbonate, tetrahydrofuran, acetone, tert-butanol, acetonitrile, propionitrile, and diethoxymethane.}\)

formation of the cis and trans products 10 (∼1.2:1 respectively, as their NMI salts) was complete, according to the presence of diagnostic signals for their H-3 and H-4 protons. In particular, trans-10 shows narrow doublets (\(J < 1\) Hz) at 5.6 and 3.9 ppm, and cis-10 shows wider doublets (\(J = 6\) Hz) at 5.3 and 4.8 ppm. These values are fully consistent with our spectra of isolated cis/ trans mixtures and those reported for analogous 1-oxo-2-alkyl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids found in the literature.\(^a\) Also apparent was the multiplet for trifluoroethylamine at 3.2 ppm, indicative of the elimination pathway (Scheme 2), and some unreacted imine 9. In addition, two sets of (initially) unassigned wide doublets were observed at 4.21 and 4.83 ppm (\(J = 12.0\) Hz), and at 4.59 and 4.37 ppm (\(J = 12.6\) Hz) in a 3:1 respective ratio. A gCOSY spectrum of the reaction mixture taken after 40 min of reaction time in situ (Figure 1) shows the expected cross-peaks for coupling of all eight doublets in the region of 3−6 ppm, as well as cross-peaks for the geminal dq signals (two each) for the −CH_3CF_3 substituents of cis- and trans-10.

Over the next 24 h at room temperature in dichloromethane-\(d_2\) solution, the cis/trans mixture of products 10 isomerized exclusively to the more stable trans-10 (as the NMI salt), a process promoted by NMI that we also observed later in gram-scale runs. The wide doublets disappeared, and a new singlet at 5.3 ppm became evident and grew in further over 48 h. From a later gram-scale reaction, we isolated this same byproduct, dibenzodihydrosoxocoumarin carboxylic acid 15 (diagnostic singlet at 5.3 ppm) as its NMI salt, and confirmed its structure and stereochemistry by X-ray crystallography (see the
Experimental Section). This type of HPA adduct has been reported previously\(^9\) and is a downstream result of the undesired Knoevenagel pathway illustrated in Scheme 2.

According to the mechanism proposed in Scheme 2, Knoevenagel product 12 can form from Mannich adduct 11 by loss of 2,2,2-trifluoroethylamine. Conjugate addition of a second equiv of HPA leads to two-to-one adduct 13, and then intramolecular C-acylation onto one of the anhydride carbonyl groups gives spiroanhydride 14 as a potential mixture of up to four diastereomers. Decarboxylation and O-cyclization furnishes 15. Spiro anhydrides 14 have not been previously observed in reactions of this type, but could account for the unassigned wide doublets observed by proton NMR early in the reaction course.

Calculational determination [Gaussian 09, B3LYP/6-31G(d)] of the structures of the two \(\text{trans}\) isomers of 14 was carried out, along with a calculation of the expected chemical shifts and coupling constants of the ring methines. The results are displayed in Figure 2, and the calculated structures and methodological details are provided in the Experimental Section and the Supporting Information. A close match is obtained between the calculated chemical shifts of the two \(\text{trans}\)-14 isomers and the observed values, and the respective calculated, unusually wide, vicinal coupling constants also match quite well with the observed \(J\) values. On the basis of these calculational results, the proton NMR observations over the time course of the reaction, and on the presumed mechanism (Scheme 2) for formation of 15, the wide doublets are assigned to pseudo-\(\text{trans}\)-diaxial vicinal H’s of intermediate \(\text{trans}\) spiro anhydrides 14.

An additional change in reaction conditions was made for the gram-scale preparation of 10: by conducting the initial reaction at \(-30^\circ\)C, the Knoevenagel pathway was suppressed almost

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**Scheme 2. Proposed Knoevenagel Byproduct 12 and Intermediates Leading to Dibenzodihydroisocoumarin 15**

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**Figure 1.** Reaction of homophthalic anhydride with NMI and imine 9 after 40 min. gCOSY cross-peaks for the wide doublets from the two spiro anhydride ring H’s are designated, respectively, c (red) and d (red). Cross-peaks for the respective ring proton doublets (a and b) and the \(-\text{CH}_2\text{CF}_3\) doublets-of-quartets (a’ and b’) signals for \(\text{trans}\)- and \(\text{cis}\)-10 are also designated.
entirely (Scheme 3). The reaction mixture was then stirred (NMI is still present) for a day, during which time the cis/trans mixture was cleanly converted to all-trans. NMI is well-suited for this isomerization at room temperature; analogous treatment of the mixture with triethylamine led to no isomerization. Adjustment of the pH to near the isoelectric point of the product (∼pH 4.5) caused it to precipitate, and filtration gave 10 in 84% overall yield.

What is the role of NMI in this formal cycloaddition, and how does it improve the reaction? Possibly, NMI benefits the reaction by affecting the balance between Perkin-analogous ring closure acting as an acyl transfer promoter,10,11 the resulting activated N-acylimidazolium intermediate, 16, is well-suited for ring closure to give desired product 17. In contrast, the elimination process would be suppressed, inasmuch as full alignment and conjugation of the newly forming π bond with the π systems of the benzo ring and the carbonyl group, a situation obtaining in 11, is weakened by σ bond rotation in 16. Furthermore, enolization of the anhydride carbonyl group, should this be prelude to elimination, is favored in 11, but not for the carbonyl group in 16. 4-(N,N-Dimethylamino)pyridine and related pyridines also promote the reaction (Table 1), possibly as a result of their well-established acyl transfer promoting property,12,13 whereas organic bases without this characteristic, such as N-methylmorpholine, N,N-diethylaniline, and 2,4,6-collidine, are ineffective.

We also applied the new reaction conditions (−30 °C, 2 equiv of NMI in dichloromethane solution) for the gram-scale synthesis of three other 1-oxo-2-alkyl/aryl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids of interest to us: 19, 20, and 21 (Chart 1). Preparation of the appropriate aldimine coupling

**Scheme 3. Optimized Conditions for Gram-Scale Synthesis of 10**

| 4 (1 equiv, added last) | 9 (1 equiv) | NMI (2 equiv) |
|------------------------|------------|---------------|
| O                      | N          | N              |
| OCOCH₃                 | N=C=N=CH₃ | N=CH₃         |
| 10 (2:3 cis + trans)  | 10 (trans only) |

Figure 2. Calculated and observed chemical shifts and vicinal coupling constants for the spiro anhydrides 14.

**Scheme 4. Proposed Role of NMI in the Reaction of HPA with Aldimines**

**Chart 1. Additional Examples of NMI Promoted HPA/Aldimine Cycloadditions**
partners is described in the Experimental Section. Products 19 and 20 are the precursors to carboxanilides 1 and 3, respectively. Compound 21 has been reported previously.\textsuperscript{14,15}

Finally, we developed an unusual, but effective, procedure for resolving racemic trans-10 (Scheme S) to provide the desired (+)-(3S,4S)-enantiomer. A suspension of racemic 10 and 2 equiv of commercial (1S,2S)-(−)-1-amino-2-indanol (22) in a 1:1 mixture of heptane and propanitrile was digested at reflux, cooled, and then filtered. The resulting solid was subjected to another digestion, and then the collected product was analyzed by proton NMR spectroscopy. Integration indicated that this salt comprises a two-to-one complex of trans-10 with (+)-(−)-1-Oxo-3-(pyridin-3-yl)-2-(2,2,2-trifluoroethyl)amino-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (Racemic trans-10). A solution of aldimine 9 (1.00 g, 5.3 mmol) and N-methylimidazole (0.87 g, 10.6 mmol) in 16 mL of dichloromethane was stirred for 40 min at 23 °C, and then was cooled to −30 °C (internal temperature) by using a dry ice acetone bath. Solid homophthalic anhydride (0.86 g, 5.3 mmol) was added in one aliquot, and the solid was observed to dissolve in less than 1 min. The reaction mixture was stirred for 2.5 h at −30 °C, and then the cooling bath was removed and the reaction mixture was allowed to come to room temperature and stirred for a total of 48 h. Saturated aqueous sodium chloride solution (30 mL) was added, and the resulting suspension was brought to pH 4.5 (monitored by pH meter) by addition of concentrated hydrochloric acid (37%, ~0.88 mL). The resulting suspension was stirred for 12 h and then filtered. The precipitate was collected by filtration, and the solid product was washed with ice cold water (2 × 15 mL) and pumped to dryness, affording carboxylic acid trans-10 (1.55 g, 84%), mp 229.1–230.5 °C.\textsuperscript{16} H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.40 (dd, 1 H, \(J_{H,J} = 4.8\) and 1.5 Hz, 8.08 (m, 1 H)), 7.56 – 7.45 (m, 3 H)), 7.32 (dd, 1 H, \(J_{H,J} = 8.1\) and 4.8 Hz), 7.23 – 7.26 (m, 1 H), 5.67 (d, 1 H, \(J_{H,J} = 1.5\) Hz), 4.57 (dq, 1 H, \(J_{H,J} = 15\) and 9.0 Hz), 4.18 (d, 1 H, \(J_{H,J} = 1.5\) Hz), 4.12 (dq, 1 H, \(J_{H,J} = 15\) and 9.0 Hz)).\textsuperscript{17} 13C NMR (75.4 MHz, DMSO-\(d_6\)) \(\delta\) 172.1, 164.1, 149.4, 148.2, 134.8, 134.4, 134.3, 133.5, 130.3, 128.9, 126.8, 126.0, 126.7 (q, \(J_{C,J} = 210\) Hz), 124.1, 123.9, 61.3, 51.0, 47.2 (q, \(J_{C,J} = 24.6\) Hz). HR-ESI-MS \[M + H\]^+ calcld for C\textsubscript{15}H\textsubscript{14}F\textsubscript{4}N\textsubscript{2}O\textsubscript{4}: m/z 359.0948; found, 359.0951.

2-Methyl-N-(thiophen-2-ylmethylene)propan-1-amine. Thiophene-2-carboxaldehyde (6.70 g, 60.6 mmol) was added to a solution of isobutylamine (8.91 mL, 90 mmol) in 28 mL of acetonitrile, and the solution was stirred at 23 °C for 15 h. Concentration afforded 9.6 g (96%) of the title compound as a yellow oil.\textsuperscript{16} H NMR (300 MHz, MeOH-\(d_4\)) \(\delta\) 8.34 (d, 1 H, \(J_{H,J} = 1.2\) Hz), 7.51 (dt, 1 H, \(J_{H,J} = 5.1\) and 1.2 Hz), 7.41 (dd, 1 H, \(J_{H,J} = 3.6\) and 1.2 Hz), 7.09 (dd, 1 H, \(J_{H,J} = 4.8\) and 3.6 Hz), 3.34 (dd, 1 H, \(J_{H,J} = 6.6\) and 1.2 Hz), 1.95 (app nonet, 1 H, \(J_{H,J} = 6.6\) Hz) (92%); \(13^C\) NMR (75.4 MHz, MeOH-\(d_4\)) \(\delta\) 155.7, 141.5, 131.4, 129.1, 127.3, 68.5, 29.2, 19.6; HR-ESI-MS \[M + H\]^+ calcld for C\textsubscript{15}H\textsubscript{14}F\textsubscript{4}N\textsubscript{2}O\textsubscript{4}: m/z 359.0948; found, 359.0851.

1H NMR spectroscopy. The well-separated H-3 signals for respective trans- and cis-tetrahydroisoquinolone carboxylate products 10 appear at 5.67 ppm (\(J_{f,f} = 0.9\) Hz) and 5.41 ppm (\(J_{f,f} = 6.0\) Hz), and the methyl (3 H) singlet of BHT appears at 2.23 ppm. The measured integral of the latter is corrected by the deviation of the molar equivalent amount of BHT from 0.333; here, 3.22 (measured) is corrected to 3.11. The sum of the measured integrals of the respective H-3 signals, in this case, 1.00 and 0.46, is divided into the corrected integral of BHT to give the apparent crude yield (here, 1.46:3.11 = 47%). Analogous measurements on reactions with added promoters gave the cycloadduct trans/cis ratios and the apparent yields shown in Table 1. In several cases, the initial cis/trans mixtures of 10 isomerized over the 16 h to all-trans.

(E)-2,2,2-Trifluoro-N-(pyridin-3-ylmethyle)ethanamine (9). Aqueous sodium hydroxide (11.8 g, 295 mmol) was added slowly to a (cooled (ice bath) mixture of 2,2,2-trifluoroethylamine hydrochloride (39.8 g, 295 mmol), 3-pyridinecarboxaldehyde (21 g, 196 mmol), and toluene (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then at 23 °C for 15 h. The toluene layer was separated, and the aqueous layer was washed with additional toluene (6 × 50 mL). The combined organic solution was dried over sodium sulfate and concentrated to afford 34.57 g (94%) of imine 9 as a pale yellow oil.\textsuperscript{16} H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 8.80 (d, 1 H, \(J_{H,J} = 2.1\) Hz), 8.72 (dd, 1 H, \(J_{H,J} = 4.8\) and 1.8 Hz), 8.41 (br s, 1 H), 8.20 (dt, 1 H, \(J_{H,J} = 7.8\) and 1.8 Hz), 7.39 (dd, 1 H, \(J_{H,J} = 8.1\) and 4.8 Hz), 4.18 (q, 2 H, \(J_{H,J} = 9.3\) and 1.5 Hz), \(13^C\) NMR (75.4 MHz, CDCl\textsubscript{3}) \(\delta\) 164.0, 152.5, 150.7, 134.0, 131.8, 124.3 (q, \(J_{C,J} = 275\) Hz), 123.8, 61.6 (q, \(J_{C,J} = 29.7\) Hz). HR-ESI-MS \[M + H\]^+ calcld for C\textsubscript{15}H\textsubscript{14}F\textsubscript{4}N\textsubscript{2}O\textsubscript{4}: m/z 230.5834; found, 230.5835.

(E)-2,2,2-Trifluoro-N-(3,3-dimethyl-2-oxo-4,5,6,7-tetrahydro-1H-inden-1-yl)propan-2-yn-1-amine (11). Aqueous sodium hydroxide (20.5 mg, 0.270 mmol, 1 equiv) in 2 mL of chloroform was treated with the homophthalic anhydride 4 (43.7 mg, 0.270 mmol, 1 equiv) in one aliquot. After 16 h, the reaction was concentrated and the residue was dissolved in 2 mL of MeOH-\(d_4\). Approximately 0.333 molar equiv of 2,6-di-tert-butyl-4-methylphenol (BHT) was added, in this case, 20.5 mg (0.093 mmol, 0.344 equiv), and the resulting solution was analyzed by 1H NMR spectroscopy.
chromatographed on silica by using 20:1 hexanes/acetone acid and then 12:8:1 hexanes/ethyl acetate/acidic acid as the eluant to afford 1.67 g (85%) of carboxylic acid 19, mp 165–166 °C.1H NMR (300 MHz, DMSO-d6) δ 13.16 (s, 1 H), 7.92 (dd, 1 H, J = 7.8 and 1.5 Hz), 7.49 (td, 1 H, J = 7.2 and 1.5 Hz), 7.42 (td, 1 H, J = 7.5 and 1.5 Hz), 7.35 (dd, 1 H, J = 7.2 and 1.5 Hz), 7.26 (dd, 1 H, J = 4.8 and 1.5 Hz), 6.99 (dd, 1 H, J = 3.5 and 0.5 Hz), 6.71 (dd, 1 H, J = 3.5 and 0.5 Hz), 5.85 (dt, 1 H, J = 1.5 and 7.6 Hz), 7.34 (dt, 1 H, J = 1.5 and 7.6 Hz), 7.20 (dd, 1 H, J = 1.5 and 7.5 Hz), 7.30 (dd, 1 H, J = 1.5 and 7.5 Hz), 7.20–7.24 (m, 2 H), 7.15 (s, 1 H, J = 1.5 Hz), 5.28 (s, 1 H, J = 1.5 Hz), 3.98 (d, 1 H, J = 1.5 Hz), 3.80 (s, 3 H), 3.17 (s, 1 H), C13 NMR (75.4 MHz, DMSO-d6) δ 173.1, 163.1, 149.7, 148.7, 148.4, 138.2, 136.4, 136.1, 135.0, 132.6, 131.3, 130.3, 130.1, 129.0, 128.8, 128.3, 128.1, 124.0, 123.5, 122.7, 121.2, 121.1, 110.4, 51.6, 37.4, 33.5. A sample crystallized from isopropanol gave free acid 15 (i-ProOH solvate, mp 170–171.3 °C; HR-ESI-MS [M + H]+ calcd for C24H22NO3S, 370.1079; found, 370.1059. These crystals were suitable for single-crystal X-ray analysis.

**2,2'-Trifluoroethylamine.** A mixture of 10 mg of 2,2'-trifluoroethylammonium chloride, 15 mg of solid sodium hydroxide, and 1.5 ml of dichloromethane was stirred for 13 h and then filtered and washed with a small amount of acetonitrile. The solids were washed with 50 ml of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 ml). Concentration of the ether supernatant gave 12.0 g (90%) of carboxylic acid 22. The resulting reaction mixture was allowed to cool and rest at 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 ml of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 ml). Concentration of the ether supernatant gave 12.0 g (90%) of carboxylic acid 22. The resulting reaction mixture was allowed to cool and rest at 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 ml of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 ml). Concentration of the ether supernatant gave 12.0 g (90%) of carboxylic acid 22. The resulting reaction mixture was allowed to cool and rest at 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 ml of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 ml). Concentration of the ether supernatant gave 12.0 g (90%) of carboxylic acid 22. The resulting reaction mixture was allowed to cool and rest at 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 ml of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 ml). Concentration of the ether supernatant gave 12.0 g (90%) of carboxylic acid 22. The resulting reaction mixture was allowed to cool and rest at 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 ml of acetonitrile. The organic solution was concentrated and then digested with ethyl ether (3 × 30 ml). Concentration of the ether supernatant gave 12.0 g (90%) of carboxylic acid 22. The resulting reaction mixture was allowed to cool and rest at 23 °C and was stirred for an additional 15 h. The reaction mixture was filtered, and the solids were washed with 50 ml of acetonitrile.
structures have little conformational flexibility of consequence, and only one significant conformation of either structure was located, in which the ring pucker places the pyridyl substituent pseudoaxial. The remaining rings were essentially perfectly planar. Rotation about the C3–C4 bonds and the C1–N–p bond was severely limited, so the C-3 and C-4 protons, and so was not explored. The major (2,3,S,4R) diastereomer was calculated to lie 3.3 kcal/mol lower in free energy than the minor (2R,3S,4R) diastereomer at 298 K.

Proton NMR properties were computed according to the procedures recommended by Bally and Rablen and co-worker.18,19 Chemical shifts were computed by using GIAO/WP04/cc-pVDZ and a simulated chloroform solvent (SCRF). Magnetic shielding values were converted into chemical shift values according to the equation $d = (31.8440 - S))/1.0205$, where $S$ is the magnetic shielding and $d$ the chemical shift. Coupling constants were computed in the gas phase at B3LYP/6-31G(d,p)u+1s and scaled by 0.916.20,21

## ASSOCIATED CONTENT

Supporting Information

1H and 13C NMR spectra of new compounds; calculated coordinates, chemical shifts, and coupling constants; and crystallographic details and CIF’s for (−)-10 (CCDC 1007451) and 15 (CCDC 1007452). This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: spencer.knapp@rutgers.edu.

### Notes

The authors declare no competing financial interest.

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