N-Methylimidazole Promotes The Reaction Of Homophthalic Anhydride With Imines

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N-Methylimidazole Promotes the Reaction of Homophthalic Anhydride with Imines

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*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.

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. 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. 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. 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.

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). The reaction is commonly thought to proceed by way of a Mannich intermediate 6, the amino group of which subsequently closes upon the anhydride carbynol group in a Perkin-analogous process leading to lactam acid 8. Alternatively, a more direct cycloaddition pathway leading to intermediate 7 or its tautomer has been considered. The reaction often goes well without additives or catalysts, but various improvements have been recommended. In our specific case with the N-2,2,2-trifluoroethylimine derived from pyridine-3-carboxaldehyde (i.e., 9, Table 1), the

Scheme 1. Formal Cycloaddition of Homophthalic Anhydride with Aldimines
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 standard, 2,6-di-tert-butyl-4-methylphenol (BHT), and integrating the appropriate signals, the approximate reaction yields of the desired products (10, combined) could be determined. Apparent yields for the reaction in chloroform solution without additive or with an equiv of acetic acid hovered around 50%. Among the various additives examined, 4-(N,N-dimethylamino)pyridine (NMI) led to a slight improvement (55%), whereas other amines of similar or lower basicity gave poorer yields and/or messier reaction mixtures. N-Methylimidazole (NMI), on the other hand, with a $pK_a \sim 7.0$ (for NMI·H$^+$), gave an improved yield (63%) at 1 equiv, and this could be increased to 78% at 2 equiv. Greater or lesser amounts of NMI did not help further. A wide variety of solvents were also screened. Of these, only dichloromethane gave yields comparable to those with chloroform, and thus, dichloromethane was selected as the preferred solvent and 2 equiv of NMI as the preferred additive.

The reaction of HPA 4 and imine 9 with 2 equiv of NMI in dichloromethane-d$_2$ solution was monitored in situ by proton NMR spectroscopy at room temperature. Within 2.5 min, formation of the cis and trans products 10 ($\sim 1.2:1$ 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. 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 3.9 ppm, making it $\sim 7.0$ ppm become evident and grew in further over 48 h. From a later gram-scale reaction, we isolated this same byproduct, which had a $pK_a$ of 7.0 (for NMI·H$^+$), and conformed its structure via X-ray crystallography (see the Supporting Information).

### Table 1. Effect of Additives and Solvent on the Apparent Yield of 1-Oxo-2-(2,2,2-trifluoroethyl)-3-(3-pyridyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acids 10

<table>
<thead>
<tr>
<th>base (equiv)</th>
<th>$pK_a$</th>
<th>solvent</th>
<th>NMR yield (trans/cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no base</td>
<td></td>
<td></td>
<td>47% (2.2:1)</td>
</tr>
<tr>
<td>pyridine (1.0)</td>
<td>5.2</td>
<td>CHCl$_3$</td>
<td>45% (1:1)</td>
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<tr>
<td>DABCO (1.0)</td>
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<td>b</td>
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<tr>
<td>N,N-diethylaniline (1.0)</td>
<td>7.6</td>
<td></td>
<td>b</td>
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<tr>
<td>N-methylmorpholine (1.0)</td>
<td>7.4</td>
<td></td>
<td>b</td>
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<td>9.2</td>
<td></td>
<td>55%</td>
</tr>
<tr>
<td>4-(dimethylamino)pyridine (1.0)</td>
<td>9.2</td>
<td>CH$_2$CN</td>
<td>b</td>
</tr>
<tr>
<td>4-(4-morpholino)pyridine (1.0)</td>
<td>8.0</td>
<td>CHCl$_3$</td>
<td>47%</td>
</tr>
<tr>
<td>4(1-pyrrolidino)pyridine (1.0)</td>
<td>9.6</td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td>HOAc (1.0)</td>
<td>4.8</td>
<td></td>
<td>50% (4:1)</td>
</tr>
<tr>
<td>N-methylimidazole, NMI (1.0)</td>
<td>7.0</td>
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<td>63%</td>
</tr>
<tr>
<td>NMI (1.5)</td>
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</tr>
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</tr>
<tr>
<td>NMI (1.0)</td>
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<td>b</td>
</tr>
</tbody>
</table>

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*Approximate $pK_a$ of conjugate acid. Poor yield and/or messy reaction mixture. 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 diethylether.
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 \([\text{Gaussian 09, B3LYP/6-31G(d)}]\) of the structures of the two 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 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-trans-diaxial vicinal H’s of intermediate 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 \(-30^\circ\text{C}\), the Knoevenagel pathway was suppressed almost

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 trans- and 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 (\(\sim\) pH 4.5) caused it to precipitate, and filtration gave 10 in 84% overall yield.

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 \(\pi\) bond with the \(\pi\) systems of the benzo ring and the carbonyl group, a situation obtaining in 11, is weakened by \(\sigma\) 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 (\(-30^\circ\text{C}, 2\text{ equiv of NMI in dichloromethane solution}\)) 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 and the main side reaction, Knoevenagel-type elimination (Scheme 4). Should NMI intercept Mannich intermediate 11,
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.14,15

Finally, we developed an unusual, but effective, procedure for resolving racemic trans-10 (Scheme 5) 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 propionitrile 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 dissolved in 2 mL of MeOH-d4 and then filtered. The resulting solid was subjected to chiral HPLC analysis. Likewise, the use of (1R,2R)-(−)-1-amino-2-indanol afforded 71% of the (−)-enantiomer of 10, mp 135−137 °C, also enantiomerically pure according to chiral HPLC analysis. The absolute configuration of the (−)-10 enantiomer was established unambiguously as (2R,3R) by X-ray crystallographic analysis of its salt with (R)-(−)-2-amino-1-phenylethanol. Details of these procedures are provided in the Experimental Section and in the Supporting Information.

■ CONCLUSION

N-Methylimidazole is effective as an additive in the formal cycloaddition reactions of aldimes with homophthalic anhydride, increasing both the yield and the selectivity (cyclization versus elimination), and also promoting the isomerization of cis/trans mixtures of product to all-trans. NMI may act in this instance as an acyl transfer agent, intercepting the ylic acids formed in the Knoevenagel reaction to form aldimines. The Mannich intermediate, e.g., 4, may act in this instance as an acyl transfer agent, intercepting the ylic acids formed in the Knoevenagel reaction to form aldimines. ESI-MS [M + H]+ calcd for C9H14NS, 168.0849; found, 168.0850.

Scheme 5. Resolution of Racemic 10

(35S,4S)-1-Oxo-3-thiophen-2-ylpropan-2-yl)cycloaddition of trans-10 to (E)-2,2,2-Trifluoro-N-(pyridin-3-ylmethylene)ethanamine (9). Aqueous sodium hydroxide (11.8 g, 295 mmol) was added slowly to a cooled (ice bath) mixture of 2,2,2-trifluoroethanaldehyde hydrochloride (39.8 g, 295 mmol), 3-pyridinecarboxaldehyde (21 g, 196 mmol), and tolune (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then at 23 °C for 15 h. The tolune layer was separated, and the aqueous layer was washed with additional tolune (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.

1H NMR spectroscopy. The well-separated H-3 signals for respective cis- and trans-10 were 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 mixture 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 230−235.5 °C. 1H NMR (300 MHz, CDCl3) δ 8.40 (dd, 1 H, J = 4.8 and 1.5 Hz), 8.36 (3 H, J = 2.1 Hz), 7.56−7.45 (m, 3 H), 7.32 (dd, 1 H, J = 8.1 and 4.8 Hz), 7.23−7.26 (m, 1 H), 5.67 (d, 1 H, J = 1.5 Hz), 4.57 (dq, 1 H, J = 15 and 9.0 Hz), 4.18 (d, 1 H, J = 1.5 Hz), 4.12 (dq, 1 H, J = 15 and 9.0 Hz). 13C NMR (75.4 MHz, DMSO-d6) δ 172.1, 164.6, 149.4, 148.2, 134.8, 130.8, 124.9, 124.8, 123.8, 61.6 (q, J = 29.7 Hz); HR-ESI-MS [M + H]+ calcd for C18H12F3N2O3, 342.0795; found, 342.0793.

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 mixture was stirred for 2 h, and then 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 mixture was stirred for 2 h, and then 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 mixture was stirred for 2 h, and then 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 mixture was stirred for 2 h, and then cooled to −30 °C.
chromatographed on silica by using 20:1 hexanes/acetic acid and then concentrated. Trituration of the residue over 16 h with 200 mL of ether gave a supernatant that, upon standing, deposited 580 mg of N-methylimidazolide salt of 15 as a tan solid: 1H NMR (300 MHz, MeOH-d$_4$) δ 5.90 (d, 1 H, J = 7.2 Hz), 7.97 (d, 1 H, J = 7.2 Hz), 7.29 (dd, 1 H, J = 7.2 and 1.5 Hz), 7.33 (dd, 1 H, J = 7.2 and 1.5 Hz), 6.86 (dd, 1 H, J = 6.8 and 1.5 Hz), 6.99 (dd, 1 H, J = 6.9 and 1.5 Hz), 5.11 (d, 1 H, J = 1.5 and 7.6 Hz), 7.34 (dt, 1 H, J = 1.5 and 7.6 Hz), 3.81 (dd, 1 H, J = 1.5 and 7.6 Hz), 7.30 (dd, 1 H, J = 1.5 and 7.6 Hz), 7.20−7.24 (m, 2 H), 7.15 (s, 1 H, J = 1.5 Hz), 5.28 (s, 1 H), 3.98 (d, 1 H, J = 1.5 Hz), 3.80 (s, 3 H), C 15(NM) 75.4 MHz, MeOD-d$_4$) δ 173.1, 161.3, 149.7, 148.7, 148.4, 138.2, 136.4, 136.1, 136.0, 135.5, 132.6, 131.3, 130.3, 130.1, 129.01, 128.8, 128.3, 128.1, 124.0, 123.5, 122.7, 121.1, 121.0, 114.0, 57.4, 33.4, 33.5. A sample crystallized from isopropanol gave free acid 15 (iPrOH solvate, mp 170−171°C; HR-ESI-MS [M + H]$^+$ calcd for C$_{22}$H$_{18}$NO$_3$, 344.1297; found, 344.1296. The crystals were suitable for single-crystal X-ray analysis.

### 2,2,2-Trifluorooxyamine

A mixture of 10 mg of 2,2,2-trifluoroethoxyamine chloride, 15 mg of solid sodium hydroxide, and 1.5 mL of dichloromethane-d$_2$ was stirred for 10 min. The supernatant, which contains the free base, was examined by NMR spectroscopy: 1H NMR (300 MHz, dichloromethane-d$_2$) δ 6.30 (app septet, 2 H, J = 8.3 Hz), 1.31 (br s, 2 H).

#### Resolution of racemic 10. A suspension of racemic 10 (9.0 g, 25.7 mmol, prepared as described above) and 7.68 g (50 mmol, 1.95 equiv) of (15S,2S)-(−)-trans-1-amino-2-indanol (22) in 270 mL of 1:1 propanol/heptane was heated at reflux (82°C internal temperature) for 3.5 h. The resulting suspension was cooled to 23°C over 3 h and filtered and the solids were washed with 102 mL of 1:1 propanol/heptane. The solids were digested again with 270 mL of the same solvent mixture, and after filtration and rinsing as before, the recovered solids were dried at 50°C for 15 h to afford 7.70 g of the chiral 2:1 salt, mp 176−178°C. 1H NMR (500 MHz, MeOH-d$_4$) δ 8.33 (d, 2 H, J = 5.0 Hz), 8.01 (dd, 1 H, J = 7.5 and 1.5 Hz), 7.55 (dd, 1 H, J = 7.0 and 3.0 Hz), 7.42 (td, 1 H, J = 7.5 and 1.5 Hz), 7.34−7.40 (m, 3 H), 7.20−7.30 (m, 7 H), 7.14 (dd, 1 H, J = 7.5 and 0.5 Hz), 5.60 (s, 1 H), 4.30−4.40 (m, 1 H), 3.75 (s, 1 H), 4.20−4.30 (m, 5 H), 3.75 (s, 1 H), 3.28 (dd, 2 H, J = 16 and 6.5 Hz), 2.82 (dd, 2 H, J = 16 and 6.5 Hz). This product was dissolved in 300 mL of 91% water/acetic acid and stirred for 15 h. Extraction with ethyl acetate (4×100 mL), followed by concentration in vacuo at 95°C to remove traces of acetic acid, gave 3.2 g (71% of theoretical) of resolved (+)-10, mp 134−137°C: [α]$_{D}^{20}$ + 60 (c 1.00, MeOH); analysis by chiral HPLC (Chiral Pak IC, 250 × 4.6 mm, 5 μL; mobile phase 80:20 hexane/isopropanol with 0.1% trifluoroacetic acid; flow rate 4 mL/min; enantiomers baseline separated) indicated an enantiomeric ratio 99:99. Anal. Calc. for C$_{22}$H$_{18}$NO$_3$·H$_2$O·C$_6$H$_5$NO$_2$: C, 62.89; H, 5.74; F, 16.27; N, 8.00. Found: C, 62.80; H, 5.86; F, 16.00; N, 7.82.

The identical procedure, but using instead (1R,2R)−(−)-trans-1-amino-2-indanol, racemic trans acid 10 (234 mg, 0.66 mmol) was converted to its 2:1 salt (173 mg, 80%), mp 176−178°C. Liberation of (−)-10 as above gave 82 mg (70% overall from racemic 10), mp 135−137°C: [α]$_{D}^{20}$ − 61 (c 1.00, MeOH).

#### Determination of Absolute Stereochernistry of Resolved (−)-10. A mixture of (−)-10 (200 mg, 0.57 mmol) and (R)-(−)-2-amino-1-phenylethanol (80 mg, 0.58 mmol) in 2 mL of 1:1 isopropyl alcohol/heptane was heated at reflux to produce a clear solution. The solution was allowed to cool and rest at 23°C overnight. The resulting crystals were collected by filtration and washed with a small amount of 1:1 isopropyl alcohol/heptane to afford 109 mg of the 1:1 salt (also contains 0.5% iPrOH of crystallization), mp 112−114°C. 1H NMR (500 MHz, MeOH-d$_4$) δ 8.34 (dd, 2 H, J = 4.5 and 1.5 Hz), 8.08 (dd, 1 H, J = 7.5 and 1.5 Hz), 7.55 (dt, 1 H, J = 8.0 and 1.5 Hz), 7.29−7.45 (m, 6 H), 7.25−7.28 (m, 1 H), 7.27 (dd, 1 H, J = 8 and 5 Hz), 7.14 (dd, 1 H, J = 7.5 and 1.5 Hz), 5.60 (s, 1 H), 4.83−4.86 (m, 1 H), 4.24−4.24 (m, 2 H), 3.80−3.95 (m, 0.25 H, IPA), 3.77 (s, 1 H), 3.09 (dd, 1 H, J = 12.5 and 1.5 Hz), 2.96 (dd, 1 H, J = 13 and 9.5 Hz), 1.14 (d, 1 H, J = 6.5 Hz). These crystals proved suitable for X-ray analysis (see the Supporting Information).

#### Calculational Studies. All calculations were carried out by using the Gaussian 09 software package. The geometries of the two diastereomers of 14 were optimized by using the B3LYP/6-31G(d) level of theory, followed by frequency calculations at the same level. The
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 pseudoequatorial. The remaining rings were essentially perfectly planar. Rotation about the C4−CO2H and C3−pyridyl was deemed unlikely to make a significant difference either for the energy or for the computed NMR properties of the C-3 and C-4 protons, and so was not explored. The major (S,S,S,4R) diastereomer was calculated to lie 3.3 kcal/mol lower in free energy than the minor (2R,S,S,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 $\delta = (31.8440 - S)/1.0205$, where $S$ is the magnetic shielding and $\delta$ the chemical shift. Coupling constants were computed in the gas phase at B3LYP/6-31G(d,p)ju+1s and scaled by 0.916.20,21

**ASSOCIATED CONTENT**

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.

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Notes

The authors declare no competing financial interest.

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