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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.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.

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 aldimes 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

Scheme 1. Formal Cycloaddition of Homophthalic Anhydride with Aldimines

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reaction under several literature conditions led to large amounts of an elimination pathway (see 12, Scheme 2) and associated downstream 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.

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>CHCl_3</td>
<td>47% (2.2:1)</td>
</tr>
<tr>
<td>pyridine (1.0)</td>
<td>5.2</td>
<td>&quot;</td>
<td>45% (1:1)</td>
</tr>
<tr>
<td>DABCO (1.0)</td>
<td>8.8</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>2,6-collidine (1.0)</td>
<td>7.6</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>N,N-diethylaniline (1.0)</td>
<td>6.6</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>N-methylmorpholine (1.0)</td>
<td>7.4</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>4-(dimethylamino)pyridine (1.0)</td>
<td>9.2</td>
<td>&quot;</td>
<td>55%</td>
</tr>
<tr>
<td>4-(dimethylamino)pyridine (1.0)</td>
<td>9.2</td>
<td>CH_2CN</td>
<td>&quot;</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>HOAc (1.0)</td>
<td>4.8</td>
<td>&quot;</td>
<td>36%</td>
</tr>
<tr>
<td>N-methylimidazole, NMI (1.0)</td>
<td>7.0</td>
<td>&quot;</td>
<td>63%</td>
</tr>
<tr>
<td>NMI (1.5)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>68%</td>
</tr>
<tr>
<td>NMI (0.5)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>65%</td>
</tr>
<tr>
<td>NMI (2.0)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>78%</td>
</tr>
<tr>
<td>NMI (5.0)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>53%</td>
</tr>
<tr>
<td>NMI (neat)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>NMI (1.0)</td>
<td>&quot;</td>
<td>toluene</td>
<td>&quot;</td>
</tr>
<tr>
<td>NMI (1.0)</td>
<td>&quot;</td>
<td>CH_2Cl_2</td>
<td>66%</td>
</tr>
<tr>
<td>NMI (1.0)</td>
<td>&quot;</td>
<td>14 other solvents</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

"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 diethoxymethane.

formulation 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. 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_2CF_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, dibenzodihydrocoumarin carboxylic acid 15 (diagnostic singlet at 5.3 ppm) as its NMI salt, and confirmed its structure and trans 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 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

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

![Scheme 2 diagram]

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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 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 (∼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 and the main side reaction, Knoevenagel-type elimination (Scheme 4). Should NMI intercept Mannich intermediate 11, 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...
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.24,15

Finally, we developed an unusual, but effective, procedure for resolving racemic 10 (Scheme 5) to provide the desired (+)-(3S,4S)-enantiomer. A suspension of racemic 10 and 2 equiv of commercial (15S,2S)-(−)-1-amino-2-indanol (22) in a 1:1 mixture of heptane and propionitrile was digested at reflux, filtered, and then 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 (1R,2R)-(−)-1-amino-2-indanol afforded 71% of the (−)-10 enantiomer, 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-Methylimidazolide 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 Mannich intermediate, e.g., 11, and promoting its ring closure. 1-Oxo-2-alkyl/aryl-3-aryl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids 10, 19, 20, and 21 have been prepared on a gram scale by this method.

**EXPERIMENTAL SECTION**

Estimation of Crude Cycloaddition Yields by 1H NMR Spectroscopy with BHT as Internal Standard. This example of the standard procedure used no additive. A stirred solution of aldimine 9 (50.0 mg, 0.270 mmol, 1 equiv) in 2 mL of chloroform was treated with 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-d4. 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. The well-separated H-3 signals for respective trans- and cis-tetrahydroisoquinoline-carboxylate products 10 appear at 5.67 ppm (δJ = 0.9 Hz) and 5.41 ppm (δJ = 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 cis/trans 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-ylmethylene)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 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 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.

1H NMR (300 MHz, CDCl3) δ 8.90 (d, 1 H, J = 2.1 Hz), 8.72 (dd, 1 H, J = 4.8 and 1.8 Hz), 8.41 (br s, 1 H), 8.20 (dt, 1 H, J = 7.8 and 1.8 Hz), 7.39 (dd, 1 H, J = 8.1 and 4.8 Hz), 4.18 (qd, 2 H, J = 9.3 and 1.5 Hz), 13C NMR (75.4 MHz, CDCl3) δ 164.0, 152.5, 150.7, 131.4, 130.8, 124.3 (q, J = 275 Hz), 123.8, 61.6 (q, J = 29.7 Hz); HR-ESI-MS [M + H]+ calced for C12H9F3N2O, 219.0788; found, 219.0794.

2-(2,2,2-Trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (Racemic trans-10). A solution of aldimine 9 (1.00 g, 5.3 mmol) and N-methylimidazolide (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 homopthalic 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 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 × 50 mL) and pumped to dryness, affording carboxylic acid trans-10 (1.55 g, 84%), mp 229.1–230.5 °C. 1H NMR (300 MHz, MeOH-d4) δ 8.40 (dd, 1 H, J = 4.8 and 1.5 Hz), 8.36 (dd, 1 H, J = 2.1, 7.8 Hz), 8.11–8.08 (m, 2 H), 7.56–7.45 (m, 3 H), 7.32 (dd, 1 H, J = 8.1 and 4.8 Hz), 7.23–7.26 (m, 2 H), 5.67 (d, 1 H, J = 1.5 Hz), 4.57 (dq, 1 H, J = 15 and 9.0 Hz), 4.18 (dq, 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, 164.4, 149.4, 148.2, 134.8, 134.8, 133.5, 130.3, 128.9, 128.6, 128.0, 126.7 (q, J = 210 Hz), 124.1, 129.6, 61.3, 51.0, 47.2 (q, J = 24.6 Hz); HR-ESI-MS [M + H]+ calced for C9H8F2N2O3, 215.0540; found, 215.0549.

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. 1H NMR (300 MHz, MeOH-d4) δ 8.34 (d, 1 H, J = 1.2 Hz), 7.51 (dt, 1 H, J = 5.1, 1.2 Hz), 7.41 (dd, 1 H, J = 3.6 and 1.2 Hz), 7.09 (dd, 1 H, J = 4.8 and 3.6 Hz), 3.34 (dd, 1 H, J = 6.6 and 1.2 Hz), 1.95 (app nonet, 1 H, J = 6.6 Hz), 0.92 (d, 6 H, J = 6.6 Hz). 13C NMR (75.4 MHz, MeOH-d4) δ 155.7, 141.5, 131.4, 129.1, 127.3, 68.5, 29.2, 19.6; HR-ESI-MS [M + H]+ calced for C8H9NS, 168.0849; found, 168.0850.

Scheme 5. Resolution of Racemic 10

\[ (+)-(3S,4S) \]

\[ (-)-(1R,2R) \]
chromatographed on silica by using 20:1 hexanes/acetic acid and then 12.8:1 hexanes/ethyl acetate/acetic acid to afford 1.14 g (40%) of carboxylic acid 21. A sample crystallized from methanol had mp 222.4–226.5 °C, lit.14 mp 203–204 °C.14 H NMR (300 MHz, DMSO-d6) δ 13.21 (s, 1 H), 8.00 (d, 1 H, J = 6.9 Hz), 7.22–7.46 (m, 13 H), 5.71 (s, 1 H), 4.24 (s, 1 H).15 C NMR (75.4 MHz, DMSO-d6) δ 172.5, 163.1, 142.8, 139.7, 134.3, 132.8, 132.0, 129.6, 129.3 (2 C), 129.1 (2 C), 128.5, 127.9, 127.8, 126.8 (2 C), 126.7 (2 C), 64.8, S16. HR-ESI-MS [M + H]+ calculated for C17H13F3N2O3: C, 58.29; H, 3.74; F, 16.27; N, 8.00. Found: C, 58.20; H, 3.86; F, 16.00; N, 7.82.

The identical procedure, but using instead (1R,2R)-(+)-2-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]D20 = 61 (c 1.00, MeOH).

Determination of Absolute Stereochemistry 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 was kept 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.16 H NMR (500 MHz, MeOH-d4) 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 (d, 1 H, J = 7.5 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, IPA, J = 6 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.17 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 C₃—C₄-C₆ linkage was deemed unlikely to make a significant difference for the energy or for the computed NMR properties of the C-3 and C-4 protons, and so was not explored. The major (2S,3S,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

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**Notes**

The authors declare no competing financial interest.

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