JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

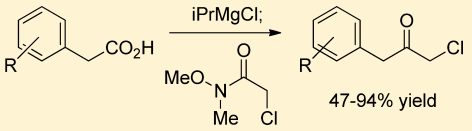
One-Step Synthesis of 1-Chloro-3-arylacetone Derivatives from Arylacetic Acids

Michael J. Zacuto,* Robert F. Dunn, and Margaret Figus

Department of Process Research, Merck Research Laboratory, Rahway, New Jersey 07065, United States

Supporting Information

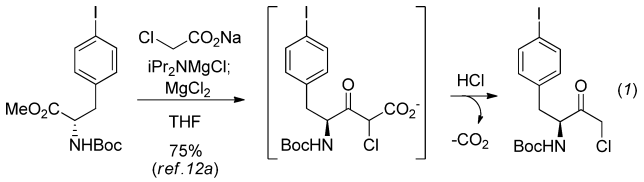
ABSTRACT: A practical one-step method has been developed to prepare α-chloroketones from readily available, inexpensive phenylacetic acid derivatives. The method utilizes the unique reactivity of an intermediate Mg−enolate dianion, which displays selectivity for the carbonyl carbon of chloromethyl carbonyl electrophiles. Decarboxylation of the intermediate occurs spontaneously during the reaction quench. The utility of the reaction products has been demonstrated through the total synthesis of the natural product cimiracemate B.



Chloromethyl ketones are valuable intermediates for the synthesis of more complex targets. For example, they serve as precursors to chiral epoxides,[1] γ-diketones,[2] and imidazoles.[3] Their importance to pharmaceuticals is illustrated by their use in the industrial syntheses of HIV protease inhibitors.[4] Furthermore, both carbons of this moiety possess potential electrophilic reactivity via either 1,2-addition to the carbonyl or S_N2 displacement of the chloride. Numerous methods have been developed to access these compounds, including but not limited to Friedel−Crafts acylation[5] or Cu-mediated coupling of arylzinc species[6] with chloroacetyl chloride. These methods are suitable for accessing acetophenone derivatives. Phenylacetone or other unconjugated ketone products are typically prepared by, for example, the addition of HCl to β-keto sulfur ylides,[7] reaction of α-diazo ketones with HCl,[8] and chlorination of methyl ketones.[9,10] During the course of our work to develop a synthesis of a recent clinical drug candidate, we required a scalable method to access α-chloroketone **3**. The use of inexpensive and readily available of 4-Cl-phenylacetic acid offered an attractive option. However, the application of reported methodologies[7−10] would have required 2−3 steps (including ester formation). In this Note we report the successful development of a novel, practical one-step procedure for this transformation from inexpensive, commercially available arylacetic acids.

Our initial studies sought to utilize an approach analogous to Masamune's β-keto ester synthesis[11] whereby the desired ketone was revealed following decarboxylation of a reactive intermediate. This has been successfully demonstrated (eq 1) in the case of α-chloro ketones using the enolate dianion derived from chloroacetic acid (**1**).[12] When applied to our substrate ester **2**, however, the yield of **3** was <5% (eq 2). We hypothesized that the di-Mg enolate anion derived from **1** was quenched by the acidic benzylic methylene protons of **2**, resulting in a net lack of desired reactivity.

Seeking to utilize the acidity of **2** and related compounds to our advantage, we examined the reversal of the nucleophile/electrophile pairing.[13] This approach had the advantage of being a one-step procedure, since esterification of the acid

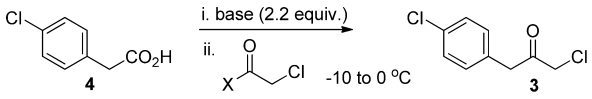


starting material was not required. The first electrophile we investigated was ethyl chloroacetate (**5**) (Table 1, entries 1−4), which afforded an optimal yield when used in combination with the dianionic-magnesium enolate derived from deprotonation with *i*-PrMgCl (entry 4). No significant impurities or byproducts were observed by HPLC assay: the mass balance was believed to be accounted for by proton transfer between ethyl chloroacetate and the enolate.[14] Use of chloroacetyl chloride as the electrophile failed to afford any desired product (Table 1, entry 5). The investigation was then extended to commercially available α-chloro Weinreb amide **6**. Deprotonation of **4** with *i*-PrMgCl followed by addition of **6** led, after appropriate quenching,[15] to **3** in 92% yield (entry 9).[16] The dramatic effect of utilizing the Weinreb amide was, to the best of our knowledge, unknown and hence became the subject of our studies.[17]

While the reaction between dianionic enolates of phenylacetic acids and Weinreb amides has been reported,[18] the use of Weinreb amides with two potentially reactive moieties (as in **6**) was unknown. Furthermore, chloroacetic acid derived electrophiles such as **5** and **6** typically afford Cl displacement products when reacted with enolates[19] and enamines.[20] This S_N2

Received: July 21, 2014
Published: September 3, 2014

Table 1. Survey of Bases and Electrophiles[a]



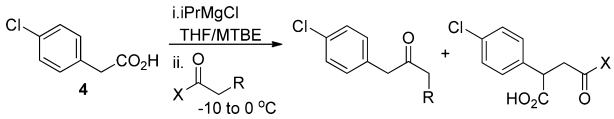
entry	base	X	yield[b]
1	*i*-Pr_2NLi	OEt (**5**)	32%
2	$(Me_3Si)_2NNa$	OEt (**5**)	–
3	*i*-Pr_2NMgCl	OEt (**5**)	62%
4	*i*-PrMgCl	OEt (**5**)	72%
5	*i*-PrMgCl	Cl	–
6	*i*-Pr_2NLi	(MeO)NMe (**6**)	14%
7	$(Me_3Si)_2NNa$	(MeO)NMe (**6**)	–
8	*i*-Pr_2NMgCl	(MeO)NMe (**6**)	64%
9	*i*-PrMgCl	(MeO)NMe (**6**)	89%

[a]Conditions: 1.3 equiv of acid, 2.6 equiv of *i*-PrMgCl, THF/MTBE; then electrophile (1.0 equiv). [b]Assay yield determined by dilution of the crude quenched reaction solution to a known volume, and comparison (using HPLC) of the product concentration to that of a standard solution of known concentration prepared from analytically pure desired product.

displacement was also observed in the pertinent example of a Li-dianion of styrylacetic acid,[21] as well as phenylacetone derivatives.[22] Thus, the use of a di-Mg-dianion with **6** engendered a unique mode of reactivity to access the 1,2-carbonyl addition product (α-Cl ketone).

To further understand the reactivity of the presumed di-Mg-dianion, we studied additional electrophiles related to **6** that can form stable tetrahedral intermediates following 1,2-carbonyl addition.[23] Examination of morpholine amide **7** (Table 2, entry

Table 2. Expanded Survey of Electrophiles[a]



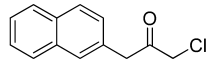
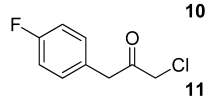
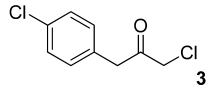
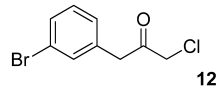
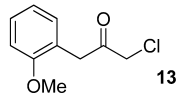
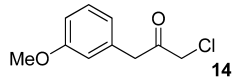
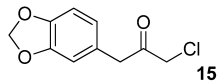
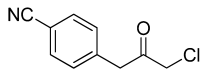
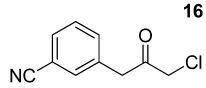
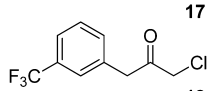
entry	base	X	R	yield[b] (C=O addition)	yield[b] (S_N2)
1	*i*-PrMgCl	morpholine	Cl (**7**)	—	50% (**8**)
2	*i*-PrMgCl	morpholine	Me (**9**)	—	—
3	*i*-PrMgCl	OEt	H	61%	—

[a]Conditions: 1.3 equiv of acid, 2.6 equiv of *i*PrMgCl, THF/MTBE; then electrophile (1.0 equiv). [b]Assay yield determined by dilution of the crude quenched reaction solution to a known volume, and comparison (using HPLC) of the product concentration to that of a standard solution of known concentration prepared from analytically pure desired product.

1) afforded carboxylic acid **8** exclusively in 50% yield.[24] This result was consistent with the lack of reactivity between **4** and morpholine amide **9** (entry 2). The observation of **8** suggested the possibility of an analogous product in the formation of **3** using **6** (Table 1, entry 9); re-examination of the HPLC and HPLC-MS data suggested that while the S_N2 product was formed as a minor impurity, the selectivity for the carbonyl addition product was >95:5. The clean reaction with ethyl acetate (Table 2, entry 3) to afford 4-Cl-phenylacetone in 61% yield was fully consistent with the results from use of ethyl chloroacetate (Table 1, entry 4).

Having established the Weinreb amide **6** as an optimal coupling partner to obtain our desired α-chloro-phenylacetone, we next investigated the scope and limitations of this process (Table 3). The reaction conditions are tolerant of aryl halides (entries 2–4), electron-donating groups (entries 5–7),

Table 3. α-Chloroketone Formation from Phenylacetic Acids[a]

entry	product	yield [b, c]
1	 **10**	92%[b]
2	 **11**	95%[b]
3	 **3**	89%[b]
4	 **12**	93%[c]
5	 **13**	75%[c]
6	 **14**	87%[c]
7	 **15**	73%[b]
8	 **16**	47%[b, d]
9	 **17**	69%[b]
10	 **18**	71%[b]

[a]Conditions: 1.3 equiv of acid, 2.6 equiv of *i*PrMgCl, THF/MTBE; then **6** (1.0 equiv). [b]Assay yield determined by dilution of the crude quenched reaction solution to a known volume, and comparison (by HPLC) of the product concentration to that of a standard solution of known concentration prepared from analytically pure desired product. [c]Product was Isolated via silica gel chromatography. [d]MTBE excluded due to solubility.

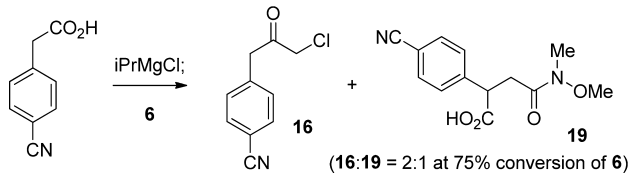
electron-withdrawing groups (entries 8–10), and *ortho*-substitution (entry 5). The presence of strong electron-donating/-withdrawing groups at the 2- and 4-positions impacted the yield, as demonstrated by the yield difference between entries 8 and 9. Use of MTBE as a cosolvent was critical for the success of these reactions, as reactions run in THF alone showed variability. The cause of this effect is not fully understood but appears to be related to stabilization of the di-Mg-enolate. Under these conditions, good to excellent yields were obtained over the wide range of aryl-substituted phenylacetic acids.[25,26]

In entries 5 and 8, where electronic effects were pronounced, byproducts resulting from S_N2 displacement of the chloride were observed. In the case of entry 5, full conversion of **6** was

dx.doi.org/10.1021/jo5016486 | J. Org. Chem. 2014, 79, 8917–8925

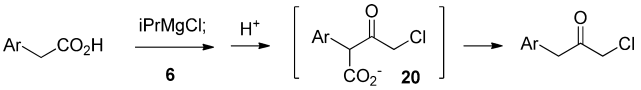
achieved and the mass balance was accounted for by a product derived from S_N2 chloride displacement.[27] For entry 8 a 2:1 ratio of **16**:**19** (by HPLC assay)[28] was obtained under our standard reaction conditions (Scheme 1).[29] In all other cases, the selectivity was ≥95:5.[30]

Scheme 1

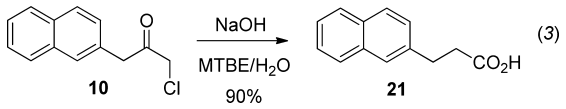


The reactions were quenched by inverse addition into a solution of 15% aqueous citric acid.[31] With the appropriate selection of aqueous volume,[32] breakdown of the tetrahedral intermediate and decarboxylation occurred spontaneously at ambient temperatures. Key to the decarboxylation was to maintain an aqueous pH of 3.5 to 5.5; at lower pH the decarboxylation was sluggish, while at higher pH Mg salts could precipitate and complicate phase separation. Decarboxylation is presumed to proceed via intermediate keto-carboxylate **20**. This latter argument is based on the observed pH-dependency of the process (Scheme 2). Following workup,[33] the crude organic stream was typically >95% pure, from which the α-chloro ketone could be crystallized or purified via column chromatography.

Scheme 2



During the workup, care was taken to not expose the product to strong bases such as hydroxide. This was based on the tendency for the α-chloro ketones to undergo selective Favorskii rearrangement (eq 3).[34] Use of weaker bases such as K_2CO_3 effectively minimized the rate of rearrangement.[35]

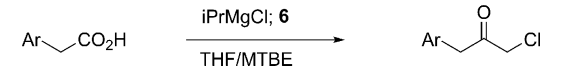


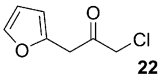
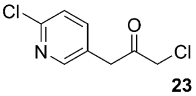
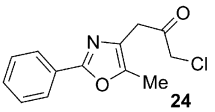
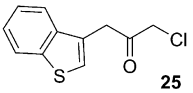
We have also extended this methodology to include aromatic heterocycles (Table 4). The reaction conditions were tolerant of furan, pyridine, benzo[*b*]thiophene, and oxazole moieties. In entry 1, the mass balance was accounted for by an S_N2 product analogous to **19**.[36] All other substrates were formed with >95:5 selectivity.

To demonstrate the utility of the 1-chloro-3-phenylacetone products, we have prepared the benzylpyrrole **26**. This class of products is of considerable interest for pharmaceutical applications.[37] Use of a modified one-pot Hantzch pyrrole synthesis[38] was adopted, whereby **11** was sequentially treated with *tert*-butyl acetoacetate and DBU, followed by the addition of MeOH and NH_4OAc to the crude unquenched reaction (Scheme 3). In the event, pyrrole **26** was obtained in 72% yield.

We have also elaborated a 1-chloro-3-phenylacetone derivative in the synthesis of the rare natural product cimiracemate B (**31**, Scheme 5).[39] Cimiracemates A[39] and B,

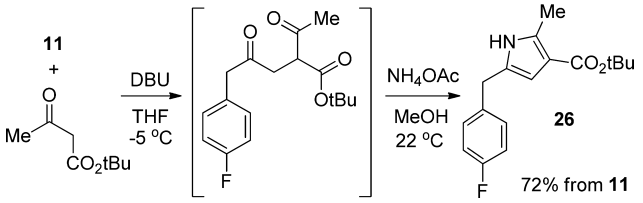
Table 4. α-Chloroketones from Heteroarylacetic Acids[a]



entry	product	yield [b]
1	 **22**	78%
2	 **23**	80%
3	 **24**	59%
4	 **25**	88%

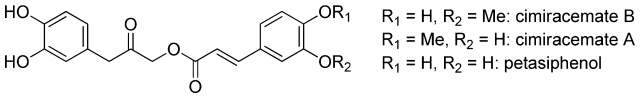
[a]Conditions: 1.3 equiv of acid, 2.6 equiv of *i*PrMgCl, THF/MTBE; then **6** (1.0 equiv). [b]Assay yield determined by dilution of the crude quenched reaction solution to a known volume, and comparison (by HPLC) of the product concentration to that of a standard solution of known concentration prepared from analytically pure desired product.

Scheme 3. Synthesis of a Benzyl Pyrrole



along with petasiphenol,[40] are structurally analogous phenylpropanoid ester components of traditional medicine[41] that exhibit antimutagenic potential (Scheme 4). In addition, the

Scheme 4. Phenylpropanoid Natural Products

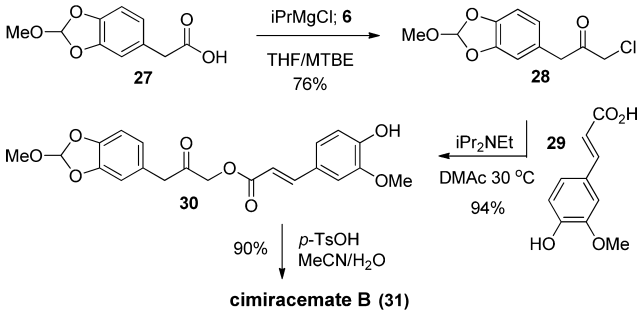


cimitracemates have been studied as a treatment for inflammation[42] and osteoporosis.[43] Phenylacetic acid **27**[44] was doubly deprotonated with *i*-PrMgCl and reacted with **6** to furnish **28** in 76% yield (Scheme 5). S_N2 displacement of the chloride with *trans*-ferulic acid (**29**), followed by ortho-ester deprotection, afforded cimiracemate B (**31**) in 85% yield over two steps.[45] This sequence should be readily adaptable to the preparation of cimiracemate A and petasiphenol.

In summary, we have demonstrated an efficient one step synthesis of 1-chloro-3-phenylacetone derivatives from phenylacetic acids. This novel method takes advantage of the reactivity of an intermediate Mg−enolate dianion, which displays selectivity for the carbonyl carbon of chloromethyl carbonyl electrophiles. Spontaneous room temperature decarboxylation

dx.doi.org/10.1021/jo5016486 | J. Org. Chem. 2014, 79, 8917−8925

Scheme 5. Total Synthesis of Cimiracemate B



during the workup contributes to the efficiency of the process. The conditions have also been extended to heterocyclic arylacetic acids. The utility of the products has been demonstrated in the preparation of a 2-benzyl-pyrrole via the Hantzch reaction and in the concise total synthesis of cimiracemate B.

EXPERIMENTAL SECTION

General Methods. Reagents and solvents were obtained from commercial sources and were used as received. Chromatography was performed using silica gel (70−230 mesh), using reagent grade solvents which were used as received. ^{1}H NMR spectra were recorded using 400 or 500 MHz spectrometers unless otherwise noted, using the $CDCl_3$ resonance as an internal standard measured at 7.26 ppm. ^{13}C NMR spectra were recorded on 100 or 125 MHz spectrometers unless otherwise noted, using the $CDCl_3$ resonance as an internal standard measured at 77.0 ppm. High-resolution mass spectrometry (HRMS) for compounds **11** and **22** was performed using a GC-TOF-MS mass spectrometer in chemical ionization (CI) mode using methane as a reagent gas.[46] High-resolution mass spectrometry for all other compounds was performed on an HPLC-TOF-ESI mass spectrometer in positive ion mode. All manipulations were carried out under an inert atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. All phenylacetic acids and *i*-PrMgCl solutions were purchased from commercial sources. Weinreb amide **6** was available from commercial sources but was prepared as described. Morpholine amides **7** and **9**, as well as authentic samples of 4-chloro-phenylacetone and 2-naphthalenepropanoic acid (**21**) were purchased from commercial sources.

HPLC assays were performed using a method with the following conditions: Ascentis Express C18 column; 4.6 mm × 100 mm, 2.7 μm particle size, 40 °C, flow rate of 1.5 mL/min consisting of a mobile phase comprised of MeCN and 0.1% by volume aqueous H_3PO_4; gradient 10% MeCN ramp to 95% MeCN over 5 min, then isocratic 95% MeCN for 2 min, with integration based on spectra recorded at the 210 nm wavelength. Assay yields were determined by quantitative dilution of the crude product stream of a known volume, followed by subjection to HPLC analysis. Comparison of the area under the curve of the diluted sample to that of a sample of known concentration prepared from the analytically pure authentic product allowed calculation of the total amount of the desired product. Alternatively, when the product was isolated via crystallization, the assay yield was determined by combining the mass of the analytically pure isolate with the desired product lost to the combined liquors (filtered supernatant plus washes). The loss was determined as described above for the assay yield, utilizing a standard prepared from the isolate.

Synthesis of 6. (MeO)MeNH$_2$Cl (107 g, 1.1 mol) was added to a stirring biphasic solution composed of MTBE (800 mL) and K_2CO_3 (166 g, 1.2 mol) in H_2O (500 mL). Chloroacetyl chloride (113 g, 79.5 mL, 1.0 mol) was added dropwise over 60 min at a rate such that T_i < 30 °C. The resulting biphasic solution was stirred for 6 h at T_i = 22 °C. The biphasic solution was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The resulting solution was concentrated to dryness to afford an oil that crystallized upon standing. The solid was slurried with hexanes (150 mL) for 2 h and filtered to afford 107 g of the desired product as a white solid which assayed at >99.9 wt % purity (78% yield). The identity was confirmed by comparison of the spectroscopic data to those of commercially available material according to ^{1}H NMR, ^{13}C NMR, and HPLC MS.

Representative Procedure for the Synthesis of α-Chloroketones.[47] A slurry of 4-chlorophenylacetic acid (2.30 g, 13.5 mmol) in MTBE (8.5 mL) was cooled to T_i = −10 °C. *i*-PrMgCl (26.0 mmol, 14.3 mL of 1.82 M in THF) was added over 30 min, maintaining T_i = −10 to −2 °C. When the addition was complete, the resulting solution was warmed to T_i = 20−25 °C and aged for 1 h. The slurry was then recooled to T_i = 0 °C, and a solution of **6** (1.375 g, 10.0 mmol) in MTBE (6 mL) was added over 15 min, maintaining T_i = 0−5 °C. Following an additional 60 min age at T_i = 0−5 °C, the HPLC assay (area under the curve) showed no remaining **6**. The reaction mixture was inverse quenched into 15% citric acid (20 mL), maintaining T_i < 35 °C. The biphasic mixture was stirred for 10 min at T_i = 22 °C to achieve complete decarboxylation. The resulting solution was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with MTBE (10 mL). The combined organic phases were washed with 10% K_2CO_3 (3 × 10 mL). The resulting organic phase was washed with brine (10 mL) and then dried over $MgSO_4$ and filtered. The filtered solution was concentrated to a solid which was slurried (with stirring) in a mixture of MTBE (0.25 mL) and *n*-heptane (10 mL) for 4 h. The slurry was filtered, and the cake was displaced with *n*-heptane (2 mL). Drying under vacuum with an N_2 sweep afforded 1.70 g of **3** as a white solid; mp = 61.8−63.1 °C. An assay of the liquors showed a loss of 0.105 g. Thus, the assay yield of **3** was 1.81 g (89% assay yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.33 (m, 2H), 7.20−7.16 (m, 2H), 4.13 (s, 2H), 3.91 (s, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 199.5, 133.4, 131.4, 130.9, 129.0, 47.8, 45.8; HRMS [M + H]$^+$ for $C_9H_8Cl_2O$ calcd 203.0025, found 203.0033.

2-(4-Chlorophenyl)-4-morpholino-4-oxobutanoic Acid (8). As in the representative procedure, a solution of 4-chlorophenylacetic acid (1.38 g, 8.2 mmol) in MTBE (10 mL) was treated with *i*-PrMgCl (16.0 mmol, 8.8 mL of 1.82 M in THF); a solution of **7** (1.63 g, 10.0 mmol) in MTBE (5 mL) and THF (2 mL) was added. Following the standard workup, the product was extracted from MTBE by washing the combined organic phases with 10% K_2CO_3 (3 × 10 mL). The resulting organic phase was discarded. The pH of the aqueous phase was adjusted to pH = 2 using 6 N HCl, and the product was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine (10 mL), then dried over $MgSO_4$, and filtered. Concentration of the CH_2Cl_2 solution, with a solvent switch to EtOH, resulted in crystallization of **8** (879 mg, 50% yield) as a white solid; mp = 157.1−158.0 °C. An assay of the liquors showed a loss of 271 mg. Thus, the assay yield of **8** was 1.15 g (50% based on theoretical 7.8 mmol); ^{1}H NMR (500 MHz, d_6-dmso): δ 12.31 (s, 1H), 7.40−7.37 (m, 2H), 7.36−7.33 (m, 2H), 3.96 (dd, J_1 = 10.4. Hz, J_2 = 4.4 Hz, 1H), 3.60−3.33 (m, 8H), 3.10 (dd, J_1 = 16.4 Hz, J_2 = 10.5 Hz, 1H), 2.59 (dd, J_1 = 16.4 Hz, J_2 = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, d_6-dmso): δ 174.4, 169.4, 138.6, 132.2, 130.3, 128.9, 66.5, 46.8, 45.6, 40.5 36.5; HRMS [M + H]$^+$ for $C_{14}H_{16}ClNO_4$ calcd 298.0841, found 298.0834.

1-Chloro-3-(naphthalen-2-yl)propan-2-one (10). As in the representative procedure, a slurry of 2-naphthylacetic acid (2.51 g, 13.5 mmol) in MTBE (9 mL) and THF (6 mL) was treated with *i*-PrMgCl (26.0 mmol, 14.3 mL of 1.82 M in THF); a solution of **6** (1.375 g, 10.0 mmol) in MTBE (5 mL) and THF (2 mL) was added. Following the typical workup, the dried, filtered solution was concentrated to a solid which was slurried (with stirring) in a mixture of MTBE (1 mL) and *n*-heptane (19 mL) for 4 h. Filtration afforded 1.835 g of **10** as a white solid; mp = 84.2−85.1 °C. An assay of the liquors showed a loss of 0.167 g. Thus, the assay yield of **10** was 2.00 g (92% assay yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86−7.78 (m, 3H), 7.72−7.68 (m, 1H), 7.53−7.45 (m, 2H), 7.33 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H), 4.15 (s, 2H), 4.06 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz,

dx.doi.org/10.1021/jo5016486 | J. Org. Chem. 2014, 79, 8917−8925

$CDCl_3$): δ 199.8, 133.4, 132.5, 130.3, 128.6, 128.3, 127.6, 127.6, 127.1, 126.4, 126.0, 47.7, 46.9; HRMS $[M + H]^+$ for $C_{13}H_{11}ClO$ calcd 219.0571, found 219.0573.

1-Chloro-3-(4-fluorophenyl)propan-2-one (11). As in the representative procedure, a solution of 4-fluorophenylacetic acid (1.815 g, 11.78 mmol) in MTBE (6.5 mL) was treated with *i*-PrMgCl (22.7 mmol, 12.5 mL of 1.82 M in THF); a solution of **6** (1.20 g, 8.72 mmol) in MTBE (4.5 mL) was added. After typical workup, the filtered solution was diluted to a 50 mL total in a volumetric flask and assayed for a 1.548 g total (95% assay yield). Concentration to dryness afforded a solid that was slurried in *n*-heptane (3 mL) for 2 h. Filtration afforded 1.40 g of **11** as a white solid; mp = 38.3−40.6 °C. An assay of the liquors showed a loss of 0.148 g of **11**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22−7.16 (m, 2H), 7.07−7.00 (m, 2H), 4.11 (s, 2H), 3.88 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.5, 161.9 (d, J_{C-F} = 245.9 Hz), 130.9 (d, J_{C-F} = 8.1 Hz), 128.5 (d, J_{C-F} = 3.6 Hz), 115.4 (d, J_{C-F} = 21.7 Hz), 47.7, 45.4 ; HRMS $[M + H]^+$ for C_9H_8ClFO calcd 187.0320, found 187.0325.

1-(3-Bromophenyl)-3-chloropropan-2-one (12). As in the representative procedure, a solution of 3-bromophenylacetic acid (2.90 g, 13.5 mmol) in MTBE (8.5 mL) was treated with *i*-PrMgCl (26.0 mmol, 14.3 mL of 1.82 M in THF); a solution of **6** (1.375 g, 10.0 mmol) in MTBE (4.5 mL) was added. After inverse quenching into citric acid (20 mL), the pH was adjusted from 3.2 to 4 0.0 by adding 5 N NaOH. Completion of the typical workup and concentration of the crude solution afforded 2.29 g of **12** (9.30 mmol, 93% yield) as an oil (**12** on occasion would crystallize to a solid that melted near ambient temperature). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (ddd, J_1 = 7.9 Hz, J_2 = 3.3 Hz, J_3 = 1.9 Hz, 1H), 7.38 (dd, J_1 = 2.3 Hz, J_2 = 1.9 Hz, 1H), 7.21 (dd, J_1 = J_2 = 7.9 Hz, 1H), 7.16−7.13 (m, 1H), 4.12 (s, 3H), 3.87 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 199.3, 135.0, 132.5, 130.6, 130.4, 128.2, 122.8, 47.8, 46.0; HRMS $[M + H]^+$ for C_9H_8BrClO calcd 246.9520, found 246. 9517.

1-Chloro-3-(2-methoxyphenyl)propan-2-one (13). As in the representative procedure, a solution of 3-methoxyphenylacetic acid (2.24 g, 13.5 mmol) in MTBE (9 mL) and THF (6 mL) was treated with *i*-PrMgCl (26.0 mmol, 14.3 mL of 1.82 M in THF); a solution of **6** (1.375 g, 10.0 mmol) in MTBE (4.5 mL) and THF (2 mL) was added. Following the typical workup, purification by silica gel chromatography (0 to 30% gradient of ethyl acetate/hexanes) afforded, after concentration, 1.49 g of **13** (7.485 mmol, 75% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (ddd, J_1 = J_2 = 8.0 Hz, J_3 = 1.6 Hz, 1H), 7.16 (dd, J_1 = 7.4 Hz, J_2 = 1.6 Hz, 1H), 6.94 (ddd, J_1 = J_2 = 7.4 Hz, J_3 = 0.9 Hz, 1H), 6.91−6.87 (m, 1H), 4.17 (s, 2H), 3.82 (s, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.8, 157.0, 131.1, 128.9, 122.1, 120.7, 110.4, 55.2, 48.2, 41.9; HRMS $[M + H]^+$ for $C_{10}H_{11}ClO_2$ calcd 199.0520, found 199.0520.

1-Chloro-3-(3-methoxyphenyl)propan-2-one (14). As in the representative procedure, a solution of 3-methoxyphenylacetic acid (2.24 g, 13.5 mmol) in MTBE (9 mL) and THF (6 mL) was treated with *i*-PrMgCl (26.0 mmol, 14.3 mL of 1.82 M in THF); a solution of **6** (1.375 g, 10.0 mmol) in MTBE (4.5 mL) and THF (2 mL) was added. Following the typical workup, purification by silica gel chromatography (0 to 30% gradient of ethyl acetate/hexanes) afforded, after concentration, 1.72 g of **14** (8.67 mmol, 87% yield) as a colorless oil. ^{1}H NMR (400 MHz, d_6-dmso): δ 7.23 (dd, J_1 = J_2 = 7.9 Hz, 1H), 6.85−6.80 (m, 1H), 6.80−6.74 (m, 2H), 4.61 (s, 2H), 3.83 (s, 2H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, d_6-dmso): δ 199.4, 159.2, 153.3, 129.3, 121.9, 115.4, 112.2, 54.9, 49.1, 45.7; HRMS $[M + H]^+$ for $C_{10}H_{11}ClO_2$ calcd 199.0520, found 199.0525.

1-(Benzo[*d*][1,3]dioxol-5-yl)-3-chloropropan-2-one (15). As in the representative procedure, a solution of 3,4-(methylenedioxy)-phenylacetic acid (3.92 g, 31.75 mmol) in MTBE (20 mL) and THF (10 mL) was treated with *i*-PrMgCl (43.5 mmol, 25.0 mL of 1.74 M in THF); a solution of **6** (2.30 g, 16.73 mmol) in THF (8 mL) was added. After 30 min, the reaction mixture was inverse quenched into 15% citric acid (30 mL), and the resulting pH = 3.2 aqueous phase was treated with 5 N NaOH until pH = 4.0. Otherwise typical workup (modified as follows: 10 mL MTBE extraction, 3 × 15 mL wash with 10% K_2CO_3 and 20 mL brine wash) afforded, after concentration, a solid which was slurried (with stirring) in a mixture of EtOAc (7 mL) and *n*-heptane (14 mL) for 2 h. The slurry was filtered, and the cake was displaced with 1:2 EtOAc/*n*-heptane (8 mL) and then *n*-heptane (6 mL). Drying under vacuum with an N_2 sweep afforded 2.12 g of **15** as a white solid; mp = 46.0−48.6 °C. An assay of the liquors showed a loss of 0.460 g. Thus, the assay yield of **15** was 2.58 g (12.13 mmol, 73% assay yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 1.8 Hz, 1H), 6.67 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 5.96 (s, 2H), 4.11 (s, 2H), 3.80 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 200.0, 148.0, 147.0, 126.2, 122.6, 109.7, 108.5, 101.1, 47.5, 46.3; HRMS $[M + H]^+$ for $C_{10}H_9ClO_3$ calcd 213.0313, found 213.0311.

4-(3-Chloro-2-oxopropyl)benzonitrile (16). As in the representative procedure, a solution of 4-cyanophenylacetic acid (1.08 g, 6.70 mmol) in THF (10 mL) was treated with *i*-PrMgCl (13.26 mmol, 7.15 mL of 1.82 M in THF); a solution of **6** (0.688 g, 5.0 mmol) in THF (4 mL) was added. After typical workup, the filtered solution was concentrated to a solid mixture of **6** and **16**. This mixture was slurried in MTBE (4 mL), and *n*-heptane (4 mL) was added over 1 h. The resulting slurry was stirred for 2 h and then filtered. The cake was displacement-washed with 1:1 MTBE/*n*-heptane (1 mL) and then *n*-heptane (1 mL). Drying under vacuum with an N_2 sweep afforded 416 mg of **16** as a white solid; mp = 95.5−96.4 °C. An assay of the liquors showed a loss of 38 mg. Thus, the assay yield of **16** was 454 mg (2.345 mmol, 47% assay yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68−7.61 (m, 2H), 7.37−7.31 (m, 2H), 4.13 (s, 2H), 4.00 (s, 2H); $^{13}C\{^1H\}$ NMR: (100 MHz, $CDCl_3$) δ 198.7, 138.1, 132.2, 130.3, 118.5, 111.2, 47.8, 46.0; HRMS $[M + H]^+$ for $C_{10}H_8ClNO$ calcd 194.0367, found 194.0364.

3-(3-Chloro-2-oxopropyl)benzonitrile (17). As in the representative procedure, a solution of 3-cyanophenylacetic acid (2.17 g, 13.5 mmol) in MTBE (10 mL) and THF (6 mL) was treated with *i*-PrMgCl (26.0 mmol, 14.3 mL of 1.82 M in THF); a solution of **6** (1.375 g, 10.0 mmol) in MTBE (5 mL) and THF (2 mL) was added. After typical workup, the filtered solution was concentrated to a solid mixture of **6** and **16**. This mixture was slurried in MTBE (6 mL) for 5 h and then filtered. The cake was displacement-washed with MTBE (3 mL). Drying under vacuum with an N_2 sweep afforded 1.005 g of **17** as a white solid; mp = 94.0−96.0 °C. An assay of the liquors showed a loss of 333 mg. Thus, the assay yield of **17** was 1.338 g (6.91 mmol, 69% assay yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63−7.57 (m, 1H), 7.54−7.50 (m, 1H), 7.49−7.44 (m, 2H), 4.14 (s, 2H), 3.98 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.0, 134.3, 134.2, 133.1, 129.6, 118.5, 112.9, 47.8, 45.5; HRMS $[M + H]^+$ for $C_{10}H_8ClNO$ calcd 194.0367, found 193.0365.

1-Chloro-3-(3-(trifluoromethyl)phenyl)propan-2-one (18). As in the representative procedure, a solution of 3-trifluoromethylphenylacetic acid (2.76 g, 13.5 mmol) in MTBE (10 mL) was treated with *i*-PrMgCl (26.0 mmol, 17.5 mL of 1.48 M in THF); a solution of **6** (1.375 g, 10.0 mmol) in THF (7 mL) was added. After typical workup, the filtered solution was concentrated to a solid which was slurried in MTBE (0.5 mL) and *n*-heptane (3 mL) and stirred for 1 h before the slurry was filtered. The cake was displacement-washed with *n*-heptane (3.5 mL). Drying under vacuum with an N_2 sweep afforded 1.674 g of **18** (7.07 mmol, 71% yield) as a white solid; mp = 41.3−43.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60−7.56 (m, 1H), 7.53−7.48 (m, 2H), 7.45−7.41 (m, 1H), 4.16 (s, 2H), 4.02 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 199.3, 133.7, 133.0, 131.1 (q, J_{C-F} = 32.5 Hz), 129.3, 126.3 (q, J_{C-F} = 3.8 Hz), 124.3 (q, J_{C-F} = 3.8 Hz), 123.9 (q, J_{C-F} = 272.3 Hz), 47.8, 46.0; HRMS $[M + H]^+$ for $C_{10}H_8ClF_3O$ calcd 237.0289, found 236.0297.

Dicyclohexylammonium 2-(4-Cyanophenyl)-4-(methoxy-(methyl)amino)-4-oxobutanoate (19). A mixture of 4-cyanophenylacetic acid and (free acid) **19** (∼100 mg) in a 1:4 HPLC ratio from the K_2CO_3 washes was diluted with EtOH (1 mL) and treated with H_2SO_4 (15 μL) to selectively esterify 4-cyanophenylacetic acid. The remaining solution of (free acid) **19** was treated with Cy_2NH (200 μL) resulted in crystallization of **19** (93 mg) as a white solid; mp = 155.7−156.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59−7.55 (m, 2H), 7.49−7.45 (m, 2H), 3.98 (dd, J_1 = 10.1 Hz, J_2 = 5.2 Hz, 1H), 3.67

dx.doi.org/10.1021/jo5016486 | J. Org. Chem. 2014, 79, 8917−8925

(s, 3H), 3.28 (dd, J_1 = 16.8 Hz, J_2 = 10.1 Hz, 1H), 3.12 (s, 3H), 2.78−2.64 (m, 2H), 1.83−1.74 (m, 2H), 1.73−1.65 (m, 2H),1.64−1.56 (m, 2H), 1.25−1.05 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.6, 172.9, 147.7, 132.0, 129.0, 118.8, 110.1, 61.1, 50.5, 49.9, 24.7, 24.4; HRMS $[M + H]^+$ $[M + H-HNCy_2]^+$ for $C_{13}H_{14}N_2O_4$ calcd 263.1026, found 263.1021.

1-Chloro-3-(furan-2-yl)propan-2-one (22). As in the representative procedure, a solution of 2-furanacetic acid (328 mg, 2.6 mmol) in MTBE (5 mL) and THF (1.5 mL) was treated with *i*-PrMgCl (5.2 mmol, 3.5 mL of 1.48 M in THF); a solution of **6** (275 mg, 2.0 mmol) in THF (1.5 mL) was added. Otherwise, typical workup (modified as follows: 5 mL of 15% aqueous citric acid, 5 mL MTBE extraction, 3 × 5 mL wash with 10% K_2CO_3 and 5 mL brine wash) afforded a solution that was diluted to a 25 mL total in a volumetric flask and assayed for a 245 mg total of **22** (1.55 mmol, 78% assay yield). Analytically pure **22** used for the assay standard was obtained from purification by silica gel chromatography (0 to 20% gradient of ethyl acetate/hexanes). Concentration under reduced pressure afforded **22** as a volatile oil which codistilled with solvents during the concentration. A small portion of analytically pure **22** (as a colorless oil) was thus obtained after thorough solvent removal. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, J_1 = 1.9 Hz, J_2 = 0.8 Hz, 1H), 6.36 (dd, J_1 = 3.2 Hz, J_2 = 1.9 Hz, 1H), 6.27−6.25 (m, 1H), 4.15 (s, 2H), 3.92 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.6, 146.7, 142.6, 110.9, 109.0, 47.8, 39.6; HRMS $[M + C_3H_5]^+$ for $C_7H_7ClO_2$ calcd 199.0520, found 199.0531.

1-Chloro-3-(6-chloropyridin-3-yl)propan-2-one (23). As in the representative procedure, a solution of 6-chloro-3-pyridineacetic acid (446 mg, 2.6 mmol) in MTBE (6 mL) and THF (2 mL) was treated with *i*-PrMgCl (5.2 mmol, 3.5 mL of 1.48 M in THF); a solution of **6** (275 mg, 2.0 mmol) in THF (2 mL) was added. Otherwise typical workup (modified as follows: 5 mL of 15% aqueous citric acid, 5 mL MTBE extraction, 3 × 5 mL wash with 10% K_2CO_3 and 5 mL brine wash) afforded a solution that was concentrated to a solid which was slurried in MTBE (0.5 mL) and *n*-heptane (5 mL) and stirred for 2.5 h before the slurry was filtered. The cake was displacement-washed with 10:1 *n*-heptane/MTBE (1 mL) and *n*-heptane (1 mL). Drying under vacuum with an N_2 sweep afforded 305 mg of **23** as a white solid; mp = 80.4−81.7 °C. An assay of the liquors showed a loss of 21 mg. Thus, the assay yield of **23** was 332 mg (1.598 mmol, 80% assay yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, J_1 = 2.5 Hz, J_2 = 0.5 Hz, 1H), 7.54 (ddt, J_1 = 8.2 Hz, J_2 = 2.5 Hz, J_3 = 0.5 Hz, 1H), 7.35−7.31 (m, 1H), 4.15 (s, 2H), 3.95 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.9, 150.6, 150.2, 140.0, 127.6, 124.3, 47.8, 42.3; HRMS $[M + H]^+$ for $C_8H_7Cl_2NO$ calcd 203.9977, found 203.9978.

1-Chloro-3-(5-methyl-2-phenyloxazol-4-yl)propan-2-one (24). As in the representative procedure, a solution of 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetic acid (565 mg, 2.6 mmol) in MTBE (6 mL) and THF (2 mL) was treated with *i*-PrMgCl (5.2 mmol, 3.0 mL of 1.74 M in THF); a solution of **6** (275 mg, 2.0 mmol) in THF (2 mL) was added. Otherwise typical workup (modified as follows: 3.5 mL of 15% aqueous citric acid followed by pH adjustment to 4.0 using 5 N NaOH, 5 mL MTBE extraction, 3 × 5 mL wash with 10% K_2CO_3 and 5 mL brine wash) afforded a solution that was concentrated to a solid which was slurried in 10:1 *n*-heptane/CH_2Cl_2 (2 mL) for 4 h and then filtered. The cake was displacement-washed with 10:1 *n*-heptane/CH_2Cl_2 (1 mL) and then *n*-heptane (1 mL). Drying under vacuum with an N_2 sweep afforded 203 mg of **24** as a white solid; mp = 73.4−77.4 °C. An assay of the liquors showed a loss of 90 mg. Thus, the assay yield of **24** was 332 mg (1.17 mmol, 59% assay yield). ^1H NMR (400 MHz, $CDCl_3$): δ 8.00−7.94 (m, 2H), 7.47−7.41 (m, 3H), 4.30 (s, 2H), 3.77 (s, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.6, 160.0, 146.1, 130.1, 128.7, 128.4, 127.3, 126.0, 48.1, 37.9, 10.3; HRMS $[M + H]^+$ for $C_{13}H_{12}ClNO_2$ calcd 250.0629, found 250.0624.

1-(Benzo[*b*]thiophen-3-yl)-3-chloropropan-2-one (25). As in the representative procedure, a solution of 2-benzo[*b*]thiophen-3-ylacetic acid (500 mg, 2.6 mmol) in MTBE (5 mL) was treated with *i*-PrMgCl (5.2 mmol, 3.5 mL of 1.48 M in THF); a solution of **6** (275 mg, 2.0 mmol) in THF (2 mL) was added. Otherwise typical workup (modified as follows: 5 mL of 15% aqueous citric acid, 5 mL MTBE extraction, 3 × 5 mL wash with 10% K_2CO_3 and 5 mL brine wash) afforded a solution that was diluted to a 25 mL total in a volumetric flask and assayed for a 393 mg total of **25** (1.75 mmol, 88% assay yield).

An unoptimized crystallization (to afford pure **25** used for the HPLC standard solution) was performed as follows: The solution was concentrated to dryness, affording a yellow oil. Purification by silica gel chromatography (0 to 15% gradient of ethyl acetate/hexanes) afforded, after concentration of pure fractions, 355 mg of **25** that crystallized upon standing. The solid was slurried in *n*-heptane and then filtered to afford pure **25** as a white solid; mp = 59.8−61.8 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.01−7.95 (m, 1H), 7.77−7.70 (m, 1H), 7.57 (s, 1H), 7.42−7.34 (m, 2H), 4.72 (s, 2H), 4.18 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 198.9, 139.4, 138.7, 128.4, 125.5, 124.3, 124.0, 122.8, 122.1, 49.0, 38.9; HRMS $[M + H]^+$ for $C_{11}H_9ClOS$ calcd, 225.0135 found 225.0143.

Synthesis of *tert*-Butyl 5-(4-Fluorobenzyl)-2-methyl-1*H*-pyrrole-3-carboxylate (26). A solution of the chloroketone **11** (560 mg, 3.0 mmol) in THF (4 mL) was cooled to T_i = −10 °C. Separately, a solution of *tert*-butyl-acetoacetate (996 mg, 6.3 mmol) in THF (6 mL) was treated with DBU (932 mg, 6.12 mmol) and aged at T_i = 22 °C for 30 min. The *tert*-butyl-acetoacetate/DBU solution was then added to **11** over 30 min, maintaining T_i = −8 to −2 °C. After 20 min, HPLC assay (area under the curve) showed >98% conversion of **11**. NH_4OAc (694 mg, 18 mmol) and MeOH (5 mL) were added, and the resulting solution was warmed to T_i = 22 °C. After 1 h, an HPLC assay showed complete conversion of the intermediate to the desired product. The reaction was quenched with H_2O (7 mL) and diluted with EtOAc (25 mL). The resulting solution was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with EtOAc (5 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, and filtered. Dilution to a 100 mL total (in a volumetric flask) allowed (via comparison of the area under the curve of a diluted sample to that of a sample of known concentration prepared from analytically pure authentic product) an assay for 623 mg of **26** (2.15 mmol, 72% assay yield).

An unoptimized crystallization was performed as follows: The solution was concentrated to dryness, affording a yellow-orange solid. This was slurried, with stirring, in MTBE (1 mL) to afford a thick heterogeneous solution. After 2 h of stirring at T_i = 22 °C, heptane (6 mL) was added over 3 h. The slurry was filtered, and the cake was displacement-washed with 6:1 heptane/MTBE (2 mL), followed by heptane (2 mL). Drying under vacuum with an N_2 sweep afforded analytically pure **26** as a white solid; mp = 95.5−96.4 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.17−7.11 (m, 2H), 7.00−6.94 (m, 2H), 6.25 (d, J = 2.8 Hz, 1H), 3.84 (s, 2H), 2.42 (s, 3H), 1.54 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 165.2, 161.7 (d, J_{C-F} = 244.4 Hz), 134.6 (d, J_{C-F} = 3.3 Hz), 134.3, 130.0 (d, J_{C-F} = 8.0 Hz), 128.2, 115.4 (d, J_{C-F} = 21.4 Hz), 113.3, 108.5, 79.2, 33.0, 28.5, 13.3; HRMS $[M + Na]^+$ for $C_{17}H_{20}FNO_2$ calcd 312.1370, found 312.1374.

Synthesis of Cimiracemate B. A solution of 3,4-dihydroxyphenyl acetic acid (1.0 g, 5.95 mmol) was dissolved in trimethyl orthoformate (80 mL). *p*-Toluenesulfonic acid hydrate (1.13 g, 5.95 mmol) was added. The resulting solution was heated to T_i = 85 °C for 3 h, with distillation of MeOH, at which point an HPLC assay (area under the curve) showed >95% conversion of starting material. The mixture was cooled to T_i = 22 °C and further concentrated under reduced pressure to an ∼5 mL total volume. EtOAc (10 mL) was added to the homogeneous solution, followed by 10% aqueous K_2CO_3 (10 mL), and the biphasic solution was stirred for 5 min before transfer to a separatory funnel. The phases were separated, and the organic phase was discarded. The aqueous phase pH was adjusted to pH 3.0 using 6 N HCl. The product was back extracted from the aqueous phase with EtOAc (2 × 10 mL). The combined organic phase was dried over $MgSO_4$ and filtered. Concentration afforded 0.98 g of **27** as an oil that crystallized upon standing (78%); white solid; mp = 121.9−123.0 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 6.86−6.80 (m, 3H), 6.77 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 3.58 (s, 2H), 3.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 178.0, 146.3, 145.4, 126.8, 122.6, 119.3, 109.4, 108.0,

dx.doi.org/10.1021/jo5016486 | J. Org. Chem. 2014, 79, 8917−8925

50.0, 40.6; HRMS $[M + H]^+$ for $C_{10}H_{10}O_5$ calcd 211.0601, found 211.0607.

A solution of **27** (420 mg, 2.0 mmol) in MTBE (3 mL) and THF (2.5 mL) was cooled to T_i = −10 °C. *i*-PrMgCl (2.3 mL of 1.72 M in THF) was added over 30 min, maintaining T_i = −10 to −3 °C. When the addition was complete, the resulting light slurry was warmed to T_i = 20−25 °C and aged for 1 h. The slurry was then recooled to T_i = 0 °C, and a solution of the Weinreb amide in THF (1 mL) was added over 10 min, maintaining T_i = 0−5 °C. After 30 min, an additional charge of **6** (28 mg, 0.2 mmol) was added as a solid. Following an additional 30 min, the mixture was inverse quenched into cold 15% citric acid (2.75 mL), resulting in an aqueous phase of pH 3.6. A few drops of 5 N NaOH were added until pH = 4. The biphasic mixture was stirred for 2 h at T_i = 22 °C to achieve complete decarboxylation. The resulting solution was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with MTBE (3 mL). The combined organic phases were washed with 10% K_2CO_3 (3 × 4 mL). The resulting organic phase was washed with brine (4 mL), then dried over $MgSO_4$, and filtered. The filtered solution was concentrated to an oil (362 mg) that slowly crystallized upon standing. Purification by silica gel chromatography (0 to 20% gradient of ethyl acetate/hexanes) afforded, after concentration, 319 mg of **28** as a colorless oil (76% based on 1.74 mmol of **6**). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 6.72 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 4.11 (s, 2H), 3.82 (s, 2H), 3.42 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 199.8, 146, 119.4, 109.3, 108.2, 50.1, 47.5, 46.3; HRMS $[M + H]^+$ for $C_{11}H_{11}ClO_4$ calcd 243.0419, found 243.0424.

i-Pr_2NEt (1.97 mmol, 344 μL) was added to a solution of *trans*-ferulic acid **29** (2.11 mmol, 411 mg) in DMAc (1.0 mL), and the resulting solution was aged at T_i = 30 °C for 20 min. Ketone **28** (1.23 mmol, 300 mg) was added dropwise as a solution in DMAc (1.5 mL). After 18 h, HPLC assay (area under the curve) showed that the ratio SM/prod was 8:92. A solution of *trans*-ferulic acid **29** (54 mg, 0.28 mmol) and *i*-Pr_2NEt (32 mg, 0.25 mmol) in DMAc (0.25 mL) was prepared as above and then added to the reaction. After an additional 16 h, an HPLC assay showed >99% conversion of **28**.

The reaction was inverse-quenched into a biphasic solution comprised of EtOAc (5 mL), saturated aqueous NH_4Cl (6 mL), and water (2 mL). The resulting solution was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with EtOAc (3 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (4 mL), followed by a brine wash (3 mL). The organic phase was dried over $MgSO_4$ and filtered. Dilution to a 50 mL total (in a volumetric flask) allowed (via comparison of the area under the curve of a diluted sample to that of a sample of known concentration prepared from analytically pure authentic product) an assay for 467 mg of **30** (94% assay yield).

The EtOAc solution was concentrated to an ∼1 mL total volume under reduced pressure. Heptane (1 mL) was added. The resulting solution was heated to T_i = 45 °C and seeded. The solution was gradually cooled over 30 min to T_i = 22 °C. After 1 h, a seed bed had formed. Heptane (4 mL) was added over 1 h. The resulting solution was then aged an additional 1 h, at which point an HPLC assay showed the product loss to the supernatant was 4.93 mg/mL. The slurry was filtered, and the cake was displacement-washed with heptane (1 mL). Drying under vacuum with an N_2 sweep afforded 444 mg of **30** as a white solid (94%); mp = 110.8−113.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 15.9 Hz, 1H), 7.09 (dd, J_1 = 8.3 Hz, J_2 = 1.9 Hz, 1H), 7.04 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.85 (s, 1H), 6.84 (d, J = 7.4 Hz, 1H), 6.79 (d, J = 1.7 Hz, 1H), 6.73 (dd, J_1 = 8.0 Hz, J_2 = 1.7 Hz, 1H), 6.36 (d, J = 15.9 Hz, 1H), 5.87 (s, 1H), 4.81 (s, 2H), 3.93 (s, 3H), 3.71 (s, 2H), 3.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 201.7, 166.3, 148.3, 146.8, 146.4, 146.3, 145.3, 126.6, 126.4, 123.3, 122.7, 119.3, 114.7, 113.9, 109.5, 109.4, 108.2, 67.4, 55.9, 50.0, 45.8; HRMS $[M + Na]^+$ for $C_{21}H_{20}O_8$ calcd 423.1050, found 423.1051.

A solution of **30** (140 mg, 0.35 mmol) in MeCN (2 mL) and H_2O (2 mL) was prepared, to which *p*-toluenesulfonic acid hydrate (20 mg, 0.1 mmol) was added. The resulting solution was heated to T_i = 45 °C (under N_2 with a vent to remove evolved MeOH). After 4 h, an HPLC assay (area under the curve) suggested complete conversion of **30**. The reaction was cooled to T_i = 22 °C and quenched with 160 μL of saturated aqueous $NaHCO_3$, resulting in pH = 6. EtOAc (3 mL) was added, and the mixture was stirred for 5 min before being transferred to a separatory funnel. The phases were separated, and the aqueous phase was extracted with EtOAc (3 mL). The combined organic phases were washed with brine (3 mL), then dried over $MgSO_4$, and filtered. Concentration under reduced pressure afforded a pale yellow oil, which began to crystallize upon standing. The resulting solid was slurried with 9:4 heptane/CH_2Cl_2 (1.6 mL), with stirring, for 4 h. The slurry was filtered, and the cake was displacement-washed with 9:4 heptane/CH_2Cl_2 (0.5 mL) followed by heptane (0.5 mL). Drying under vacuum with an N_2 sweep afforded 113 mg of **31** (90.4%). ^{1}H NMR (400 MHz, CD_3OD): δ 7.66 (d, J = 16.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.09 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 2.0 Hz, 1H), 6.57 (dd, J_1 = 8.2 Hz, J_2 = 2.1 Hz, 1H), 6.42 (d, J = 16.0 Hz, 1H), 3.90 (s, 3H), 3.64 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ 204.6, 168.3, 150.8, 149.4, 147.7, 146.5, 145.6, 127.6, 126.0, 124.3, 122.0, 117.6, 116.6, 116.5, 114.5, 111.8, 68.5, 56.5, 46.3; HRMS $[M + H]^+$ for $C_{19}H_{18}O_7$ calcd 359.1125, found 359.1131.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C spectra of compounds **3**, **6**, **8**, **10**−**19**, and **22**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: michael_zacuto@merck.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully thank Dr. Ross Yang (HRMS) and Dr. Peter Dormer (NMR) for assistance with compound characterization.

■ REFERENCES

(1) Via asymmetric ketone hydrogenation; see: Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373.

(2) Tasuda, M.; Tsuji, S.; Shigeyoshi, Y.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 7440.

(3) For large scale examples, see: (a) Li, B.; Chiu, C. K.- F.; Hank, R. F.; Murry, J.; Roth, J.; Tobiassen, H. *Org. Process Res. Dev.* **2002**, *6*, 682. (b) Ruck, R. T.; Huffman, M. A.; Stewart, G. A.; Cleator, E.; Kandur, W. V.; Kim, M. M.; Zhao, D. *Org. Process Res. Dev.* **2012**, *16*, 1329.

(4) (a) Ikunaka, M.; Matsumoto, J.; Fujima, Y.; Hirayama, Y. *Org. Process Res. Dev.* **2002**, *6*, 49 (Nelfinavir). (b) Göbring, W.; Gokbale, S.; Hilpert, H.; Roessler, F.; Schlageter, M.; Vogt, P. *Chimia* **1996**, *50*, 532 (Saquinavir). For a more general discussion, see: (c) Honda, Y.; Katayama, M.; Kojima, M.; Suzuki, T.; Kishibata, N.; Izawa, K. *Org. Biomol. Chem.* **2004**, *2*, 2061.

(5) For example, see: (a) Simonoff, R.; Hartung, W. H. *J. Am. Pharm. Assn.* **1946**, *35*, 306. (b) Rothstein, E.; Saville, R. W. *J. Chem. Soc.* **1949**, 1961.

(6) Rosen, J.; Steinhuebel, D.; Palucki, M.; Davies, I. *Org. Lett.* **2007**, *9*, 667.

(7) Wang, D.; Schwinden, M. D.; Radesca, L.; Patel, B.; Kronenthal, D.; Hsing Huang, M.-H.; William, A.; Nugent, W. A. *J. Org. Chem.* **2004**, *69*, 1629.

(8) McPhee, W. D.; Klingsberg, E. *J. Am. Chem. Soc.* **1944**, *66*, 1132.

(9) For example (via a silyl enol ether), see: (a) Maggiotti, V.; Wong, J.-B.; Razet, R.; Cowley, A. R.; Gouverneur, V. *Tetrahedron: Asymmetry*

2002, *13*, 1789 and a related methodology (via a Meldrum's acid adduct). (b) Horak, R. M.; Learmonth, R. A.; Maharaj, V. J. *Tetrahedron Lett.* **1995**, *36*, 1541.

(10) Other examples of formation of chloromethyl ketones from carboxylic acids include reaction of HCl with an α-diazo ketone; for example, see: (a) Miyahara, Y. *J. Org. Chem.* **2006**, *71*, 6516. (b) Bierer, D. McClure, A.; Fu, W.; Achebe, F.; Ladouceur, G. H.; Burke, M. J.; Bi, C.; Hart, B.; Dumas, J.; Sibley, R.; Scott, W. J.; Johnson, J.; Asgari, D. WO2003027085. For the reaction of chloro-methyllithium with esters, see, for example: (c) Tarhouniu, R.; Kirschleger, M.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1984**, *25*, 835. (d) Breitfelder, S.; Schuemacher, A. C.; Rolle, T.; Kikuchi, M.; Hoffmann, R. W. *Helv. Chim. Acta* **2004**, *87*, 1202. For a similar approach to α-Br ketones, see: (e) Chen, P.; Cheng, P. T. W.; Spergel, S. H.; Zahler, R.; Wang, X.; Thottathil, J.; Barrish, J. C.; Polniaszek, R. P. *Tetrahedron Lett.* **1997**, *38*, 3175. For an excellent overview, see: (f) Ram, R. N.; Manoj, T. P. *J. Org. Chem.* **2008**, *73*, 5633.

(11) For a recent example, see: (a) Hanselmann, R.; Job, G. E.; Johnson, G.; Lou, R.; Martynow, J. G.; Reeve, M. M. *Org. Process Res. Dev.* **2010**, *14*, 152.

(12) (a) Yan, J.; Huang, N.; Li, S.; Yang, L.- M.; Xing, W.; Zheng, Y.-T.; Hu, Y. *Bioorg. Chem. Med. Chem. Lett.* **2012**, *22*, 1976. (b) Amano, S.; Taoka, N.; Mitsuda, M.; Inoue, K. WO2000048997. (c) Houpis, I. N.; Liu, R.; Liu, L.; Wang, Y.; Dong, N.; Zhao, X.; Zhang, Y.; Xiao, T.; Wang, Y.; Depre, D.; Nettekoven, U.; Vogel, M.; Wilson, R.; Collier, S. *Adv. Synth. Catal.* **2013**, *355*, 1829. (d) Wang, X.; Thottathil, J. K.; Polniaszek, R. P. *Synlett* **2000**, 902.

(13) A related strategy using α-Cl esters as nucleophiles has been described: Nishiyama, A.; Nagashima, N. WO2006051723.

(14) The reaction profile was clean by HPLC, containing only product and starting materials. Furthermore, subjection of the isolated product ketones to the reaction conditions resulted in rapid decomposition/consumption of the respective ketone. This suggested stability of the tetrahedral intermediate prior to quench.

(15) See Experimental Section and Supporting Information for details.

(16) Unless otherwise noted, yields in Tables 1− 4 were determined by HPLC assay yield (see footnote b in Tables 1− 4). Standard solutions were prepared from analytically pure, crystalline samples. The propensity of the 1-chloro-3-arylacetone products in this manuscript to crystallize on silica gel columns complicated the ability to obtain yields that accurately reflected the reaction efficiency. Most of the crude chloro-ketone product streams afforded solid material following solvent removal. These crude solids were then recrystallized to obtain >99% pure material, without optimization to minimize supernatant losses.

(17) Reference 13 does not claim Weinreb amides among the suitable electrophiles.

(18) For example, see: Barton, P. J.; Clarke, D. S.; Davies, C. D.; Hargreaves, R. B.; Pease, J. E.; Rankine, M. J. WO/2004/011410.

(19) (a) Jeong-il Park, J.; Tian, G. R.; Kim, D. H. *J. Org. Chem.* **2001**, *66*, 3696. (b) Meyers, A. I.; Berney, D. *J. Org. Chem.* **1989**, *54*, 4673. Malonate anions exhibit similar reactivity: for example, see: (c) Metten, B.; Kostermans, M.; Van Baelen, G.; Smet, M.; Dehaen, W. *Tetrahedron* **2006**, *62*, 6018. One example of Li-dianions derived from *tert*-butyl acetoacetate reported products derived from 1,2-addition to the carbonyl, with significantly higher yields obtained using methyl chloroacetate compared to using **6**; see: (d) Wolberg, M.; Hummel, W.; Müller, M. *Chem.—Eur. J.* **2001**, *7*, 4652.

(20) Overman, L. E.; Wolfe, J. P. *J. Org. Chem.* **2002**, *67*, 6421.

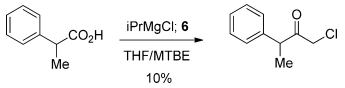
(21) Trabulsi, H.; Rousseau, G. *Synth. Commun.* **2011**, *41*, 2123.

(22) Verniest, G.; De Kimpe, N. *Synlett* **2003**, 2013.

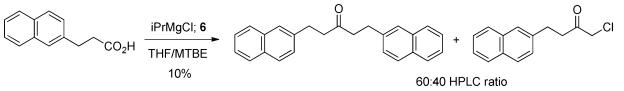
(23) (a) Martin, R.; Romea, P.; Tey, C.; Urpf, F.; Vilarrasa, J. *Synlett* **1997**, 1414. (b) Kurosu, M.; Kishi, Y. *Tetrahedron Lett.* **1998**, *39*, 4793. For a recent example utilizing morpholine amides on a large scale, see: (c) Peters, R.; Waldmeier, P.; Joncour, A. *Org. Process Res. Dev.* **2005**, *9*, 508.

(24) Similar reactivity has been reported with arylacetic esters; see: (a) Eggenweiler, H.-M.; Sirrenberg, C.; Buchstaller, H.-P. WO2011060873. For related reactivity with malonates, see: (b) Tius, M. A.; Busch-Petersen, J. *Synlett* **1997**, 531. (c) Tsubusaki, T.; Nishino, H. *Tetrahedron* **2009**, *65*, 9448.

(25) When the standard reaction conditions were applied to 2-phenylpropanoic acid, the desired product was formed in 10% yield. Preliminary evidence suggested incomplete deprotonation of the acid starting material. Evidence for the α-chloro ketone product was determined from HPLC-MS and ^{1}H NMR data of the crude mixture after workup.



(26) When the standard reaction conditions were applied to 3-(naphthalen-2-yl)propanoic acid, the α-chloroketone was formed as part of an inseparable mixture. Its structure was deduced from HPLC-MS and ^{1}H NMR data of the mixture. The ketone was presumably formed via dianion self-condensation, followed by decarboxylation during workup. For recent reviews on carboxylic acid ketonization, see: (a) Pham, T. N.; Sooknoi, T.; Crossley, S. P.; Resasco, D. E. *ACS Catal.* **2013**, *3*, 2456. and (b) Renz, M. *Eur. J. Org. Chem.* **2005**, 979.



(27) The HPLC ratio of products was 3:1, as determined by the area under the curve observed at 210 nm. The byproduct was identified by LCMS.

(28) HPLC conditions: Ascentis Express C18; 4.6 mm × 100 mm, 2.7 μm particle size, 40 °C, flow rate of 1.5 mL/min mobile phase comprised of MeCN and 0.1% by volume aqueous H_3PO_4; gradient 10% MeCN ramp to 95% MeCN over 5 min.

(29) The ratio was determined by HPLC as area % under the curve. **19** was isolated and characterized as its $CyNH_2$ salt.

(30) The erosion of selectivity in substrates bearing electron donating and withdrawing groups in the 2- and 4- positions is not well understood but is the focus of future studies.

(31) Direct quench was problematic due to precipitation of Mg salts under high pH conditions at the beginning of the acid addition. While other acids were examined, citric acid was preferred due to the pH of the resulting aqueous phase.

(32) See Experimental Section.

(33) In the case of a pH < 2.5, base could be added to raise the pH to 4−5 at which point decarboxylation would initiate. After removal of the aqueous phase, the organic phase was washed with base (K_2CO_3) to extract excess phenylacetic acid and any minor amounts of byproducts analogous to those in Scheme 2.

(34) Bordwell, F. G.; Scamehorn, R. C.; Springer, W. R. *J. Am. Chem. Soc.* **1969**, *91*, 2087. In this case, the addition of **10** to a biphasic solution of MTBE and 1 N NaOH resulted in quantitative conversion to **22** after 5 min. After removal of the MTBE, the aqueous phase was pH-adjusted to 3−4, from which **22** crystallized in 90% yield (eq 8).

(35) The rate of Favorskii rearrangement was < 0.5%/h during the first wash. During the second wash, with a slightly higher pH, this rate increased slightly. The use of bicarbonate as base essentially shut down the Favorskii pathway, albeit at the expense of volume productivity as extraction of the SM acid was less efficient.

(36) This was identified by mass spectrum data using HPLC-MS.

(37) For examples closely related to **27** as HIV Integrase inhibitors, see: (a) Selnick, H. G.; Hazuda, D. J.; Egbertson, M.; Guare, J. P., Jr.; Wai, J. S.; Young, S. D.; Clark, D. L.; Medina, J. C. WO 9962513 A1 19991209. For 5-HT2B and 5-HT7 receptor antagonists, see: (b) Seo, R.; Kaku, H.; Yamada, H.; Kaga, D.; Akuzawa, S. WO 2007097276 A1 20070830.

(38) Hantzsch, A. *Ber.* **1890**, *23*, 1474.

(39) (a) Chen, S.-N.; Fabricant, D. S.; Pauli, G. F.; Fong, H. H. S.; Farnsworth, N. R. *Nat. Prod. Res.* **2005**, *19*, 287. For the synthesis of cimiracemate B and further discussion of biological activity, see:

(b) Fache, F.; Suzan, N.; Piva, O. *Tetrahedron* **2005**, *61*, 5261 and references therein.
(40) Leading reference: Iriye, R.; Furukawa, K.; Nishida, R.; Kim, C.; Fukami, H. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1773.
(41) (a) Lieberman, S. A. J. *Womens Health* **1998**, *7*, 525. (b) Johnson, B. M.; van Breemen, R. B. *Chem. Res. Toxicol.* **2003**, *16*, 838. (c) Sakai, S.; Ochiai, H.; Nakajima, K.; Terasawa, K. *Cytokine* **1997**, *9*, 242.
(42) (a) Lau, A. S. Y.; Yang, L. H. C.; Chung, A. C. WO 2013132346 A2 20130912. (b) Yang, C. L. H.; Chik, S. C. C.; Li, J. C. B.; Cheung, B. K. W.; Lau, A. S. Y *J. Med. Chem.* **2009**, *52*, 6707.
(43) (a) Intelmann, D.; Schuh, M.; Stecher, G.; Abel, G.; Jakob, F.; Ebert, R.; Wuttke, W.; Seidlova-Wuttke, D. Eur. Pat. Appl. (2013), EP 2545932 A1 20130116. (b) Burdette, J. E.; Chen, S.-N.; Lu, Z.-Z.; Xu, H.; White, B. E. P.; Fabricant, D. S.; Liu, J.; Fong, H. S.; Farnsworth, N. R.; Constantinou, A. I.; Van Breeman, R. B.; Pezzuto, J. M.; Bolton, J. L. *J. Agric. Food Chem.* **2002**, *50*, 7022.
(44) Commercially available, or prepared in one step from commercially available 2-(3,4-dihydroxyphenyl)acetic acid (see Experimental Section).
(45) The ^{1}H and ^{13}C NMR spectra of the isolated product were identical to those reported for cimiracemate B (ref 32b).
(46) Use of methane as a reagent gas can lead to M^{+}, $[M + H]^{+}$, $[M + C_2H_5]^{+}$, and $[M + C_3H_5]^{+}$ radical cations.
(47) Due to solubility differences of each substrate, minor modifications (with respect to the volumes of MTBE and THF) were required for many examples in order to maintain sufficient stirring. Likewise, minor modifications were utilized for the unoptimized crystallization (as in ref 16) of many products.