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Magnesium Meerwein–Ponndorf–Verley–Oppenauer Reaction. The Origin of an Impurity in PDA-641 Batches

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Abstract:

An impurity in the initial scale-up batch of PDA-641 was identified and the pathway of its formation was established. The precursor of the impurity was formed by magnesium Meerwein-Ponndorf-Verley-Oppenauer reaction during the Grignard addition step. As a result of the investigation, the level of the impurity could be reduced 6-fold in the subsequent batch.

Introduction

Inhibitors of phosphodiesterase IV isoenzyme (PDE IV) have therapeutic advantage in the management of asthma.[1] The discovery at Wyeth-Ayerst Research of a preferential PDE-IV inhibitor, 3′-(cyclopentyloxy)-4′-methoxyacetophenone (*E*)-*O*-carbamoyloxime (PDA-641; **1**, Chart 1), generated a need for multikilogram quantities of the drug substance.

The synthetic pathway to **1** included MeMgCl addition to 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**2**, Chart 1),[2b] followed by hypochlorite oxidation, oximation, and carbamoylation (Scheme 1). The initial scale-up batch of PDA-641 contained an unknown impurity at a level of 0.50%—a borderline value for the purity requirements.[3] The impurity was difficult to remove by recrystallization. Therefore, it was necessary to identify the impurity, its source, and the way of suppressing its formation.

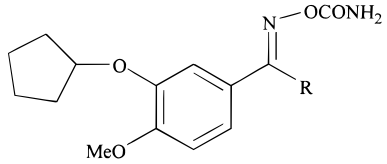
Results and Discussion

The LC–MS data suggested that the impurity might be the carbamate of the aldehyde oxime, **3** (Chart 1). Its identity was confirmed by chromatographic and spectroscopic comparison to an authentic sample of **3**. It was presumed that the precursor to impurity **3** was the analogous oxime **5** (Chart 1). In fact, it was present as the largest single impurity in all the oxime **6** (Chart 1) batches. An authentic sample of **5** was prepared from **2** and characterized spectroscopically. Once generated, **5** was converted to the carbamate **3** in the carbamoylation step.

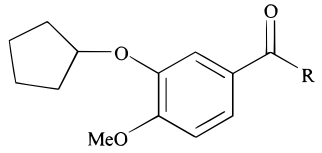
Initially, it was thought that, prior to oximation, the presence of aldehyde **2** in ketone **4** (Chart 1)[2b] solutions was the result of incomplete MeMgCl addition. Although the residual aldehyde route cannot be ruled out, there is another pathway by which the aldehyde is generated (Scheme 2).

The addition of MeMgCl to **2** is the principal reaction pathway. The formed chloromagnesium *sec*-alcoholate **7**-Mg reacts with aldehyde **2** to give the chloromagnesium alcoholate of primary benzylic alcohol **8**-Mg and ketone **4**.

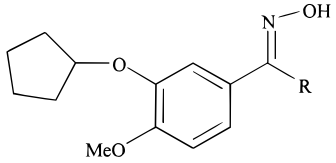
Chart 1



1 R = Me
3 R = H

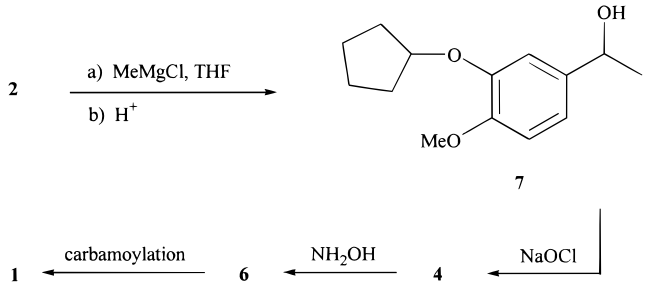


2 R = H
4 R = Me



5 R = H
6 R = Me

Scheme 1



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(1) Cavalla, D.; Frith, R. *Curr. Med. Chem.* **1995**, *2,* 561.
(2) (a) Heaslip, R. J.; Lombardo, L. J.; Golankiewicz, J. M.; Ilsemann, B. A.; Evans, D. Y.; Sickels, B. D.; Mudrick, J. K.; Bagli, J. F.; Weichman, B. M. *J. Pharmacol. Exp. Ther.* **1994**, *268*, 888. (b) Lombardo, L. J. Eur. Pat. Appl. 470 805 A1, 1992.
(3) Wyeth-Ayerst Research internal specification.

10.1021/op980078o CCC: $15.00
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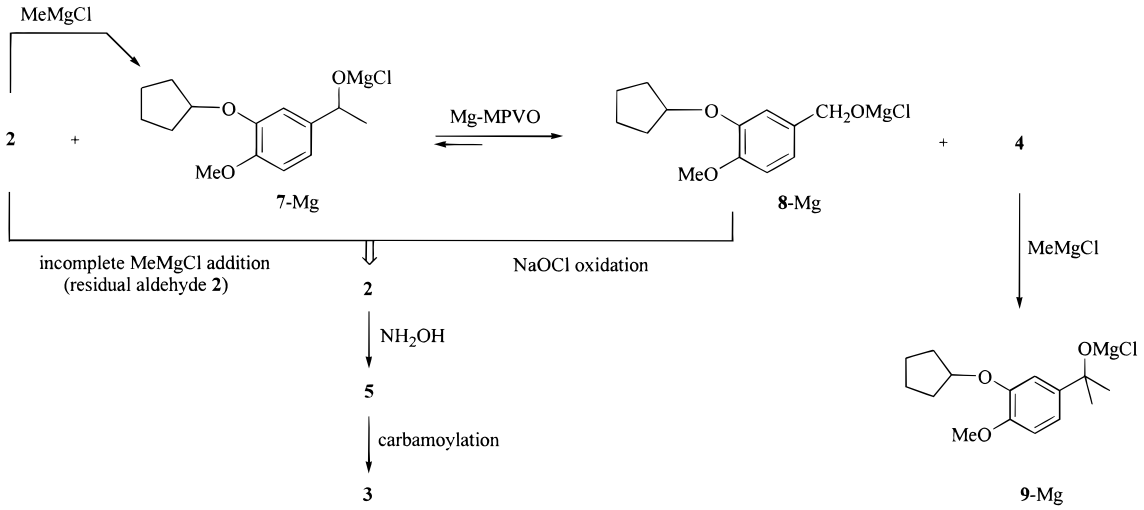
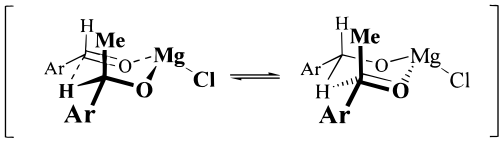
Scheme 2



Based on LC−MS mass fragmentation pattern, primary alcohol **8**, ketone **4**, and tertiary alcohol **9** were present in the batch. Synthesis of authentic samples of **8** and **9** confirmed both structures. Thus formed, primary alcohol **8** was carried over to the oxidation step, where it underwent oxidation to aldehyde **2** but not to the acid. Under hypochlorite phase-transfer conditions, primary benzylic alcohols undergo oxidation to aldehydes.[4] Finally, **2** was converted to **5** and then to **3** in the subsequent steps. To suppress formation of **3**, it was imperative to minimize generation of primary alcohol **8** at the Grignard stage.

The reaction described in Scheme 2 resembles the Cannizzaro reaction,[5] a base-catalyzed dismutation of an aromatic aldehyde.[6] It was our initial preference to use the term "magnesium-Cannizzaro reaction" as a distinction from Meerwein−Ponndorf−Verley−Oppenauer (MPVO) reactions.[7] These transformations involve hydride-transfer mechanism. However, MPVO reactions usually take place with group III and IV elements. Magnesium can be considered as a special case of MPVO reactions. Indeed, magnesium ethoxide was used by Meerwein and Schmidt to reduce benzaldehyde.[8] Marshall was the first to observe and recognize an excess of benzaldehyde as an oxidant in reactions with the Grignard reagents.[9] He also pointed out the similarities to the Cannizzaro reaction and proposed the mechanism. Later, Shankland and Gomberg[10] and Meisenheimer[11] supplied further evidence in favor of Marshall's proposal. More recently, an example of magnesium−Oppenauer oxidation was described by Byrne and Karras.[12] The reaction was also used as a method of ketone preparation.[13] We decided to use the term "Mg-MPVO reaction" because of the mechanistic similarities.[14]

Scheme 3



The MPVO transformations are equilibrium reactions which show a strong preference for the formation of primary alcoholates and ketones in equilibria involving aldehydes and secondary alcoholates.[15] The initial step involves complexation of the carbonyl group with the metal atom.[16] The activated aldehyde then accepts the hydride from the magnesium alcoholate (Scheme 3).[17]

Alkoxy groups on the aromatic ring of the hydride donor **7**-Mg facilitate hydride transfer from the benzylic position. Moreover, *para*-substitution considerably increases the reaction rate and equilibrium constant.[18] The aromatic aldehyde **2**, an acceptor, has a low reduction potential, placing it among good oxidants.[19]

It was necessary to explore some details of the Mg-MPVO reaction of **2** with **7**-Mg and MeMgCl. Product distribution data of the addition of MeMgCl to aldehyde **2** in THF showed that higher temperatures favored the formation of the primary alcohol **8** (1.2 and 9.0% at 0 and 65 °C, respectively). Lowering the temperature to −5 °C suppressed the formation of **8** to 0.5%. Addition of MeMgCl

(4) Skarzewski, J.; Siedlecka, R. *Org. Prep. Proc. Int.* **1992**, *24*, 625. The aldehyde **2** was subjected to the reaction conditions and was recovered thereafter.
(5) Gokel, G. W.; Gerdes, H. M.; Rebert, N. W. *Tetrahedron Lett.* **1976**, 653.
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Table 1. **Product distribution (HPLC area, %) in MeMgCl and 7-Mg reactions with 2**

	order of addition	reaction time (h)	temp (°C)	**8**	**7**	**9**	**2** + **4**[a]
1	MeMgCl to **2**	1	−60	0.3	74.4	0	24.5
2	MeMgCl to **2**	1	−10	0.5	96.8	0	0.7
3	MeMgCl to **2**[b]	24	20	16.2	52.4	6.5	24.1
4	MeMgCl to **2**	23[c]	0	32.7	49.4	2.2	13.2
5	MeMgCl to **2**	2	0	1.1	97.1	0.2	1.0
6	MeMgCl to **2**	0.75[d]	0	0.4	96.9	0.2	0.7
7	**2** to MeMgCl	1	0	3.2	87.6	0	8.8
8	**2** to MeMgCl	1	20	5.3	80.1	0.2	14.2[e]
9	**2** to **7**-Mg	3.75[f]	0	29.8	34.4	0	34.2
10	**2** to **7**-Mg	3.5	25	37.3	34.5	0	26.5

[a] Both **2** and **4** were inseparable under the HPLC conditions. [b] In Bu_2O/*tert*-BuOMe mixture; nonhomogeneous. [c] Total addition time. [d] MeMgCl added in 2 min. [e] Consisted of ~8.5% of **2** and 5.7% of **4** (peaks not fully resolved). [f] The reaction mixture was kept at 4 °C for 2 days.

at −60 °C, followed by quench with methanol at this temperature and then with water, gave only 0.4% of primary alcohol **8**, but it also left unreacted aldehyde (entry 1, Table 1). Tetrahydrofuran is a Lewis base[20] which decreases the electronegativity of the metal, lowering the reaction rate of hydride transfer.[12] In less complexing ethers such as Bu_2O and *t*-BuOMe, more **8** was formed (entry 3, Table 1). Interestingly, reverse addition, **2** to MeMgCl, gave more **8** than the normal addition, MeMgCl to **2** (entries 7 and 8, Table 1). Apparently, this was due to the higher viscosity of the reaction medium, especially at lower temperatures. This may also indicate relatively slow reaction rates for the addition of MeMgCl to **2**. It was observed that the product distribution depended upon the time of MeMgCl addition. The kinetics of the addition were investigated, revealing substantial formation of primary alcohol **8** when MeMgCl was added at very slow rates (entries 4−6, Table 1). Faster additions gave lesser amounts of **8**. A large excess of **2** at the beginning of MeMgCl addition shifts the Mg-MPVO equilibrium to the right side (Scheme 2). This shift is enhanced by removal of **4** due to its further reaction with MeMgCl to form **9**-Mg.[21]

The Mg-MPVO reaction was modeled using magnesium *sec*-alcoholate **7**-Mg and aldehyde **2** (entries 9 and 10, Table 1). Slow addition of the alcoholate at both 0 and 25 °C gave 30−37% of the primary alcohol **8**. During the reaction of equimolar amounts of **7**-Mg and **2** at room temperature in THF, formation of the primary alcohol **8** was initially relatively fast[22] and then slowed substantially, reaching the equilibrium (Figure 1).

The data collected during the first plant batch in conjunction with laboratory results lead to better control of the second batch. In the first pilot plant batch (A), MeMgCl was added at about −6 °C, whereas in the second batch (B),

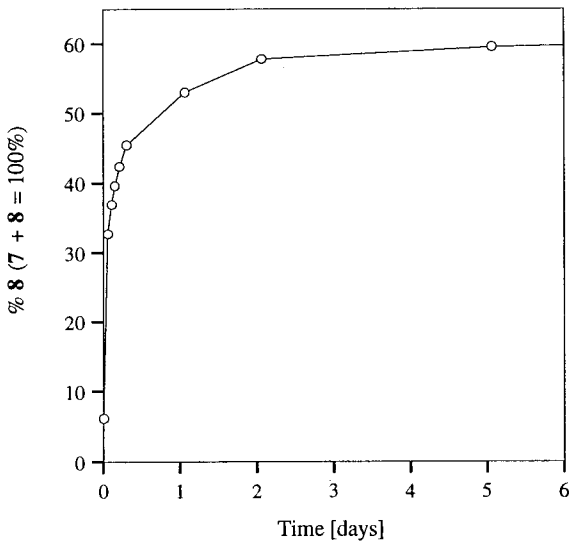

Figure 1. **Formation of 8 in the reaction of 7-Mg with 2 in THF at room temperature (HPLC area, %).**

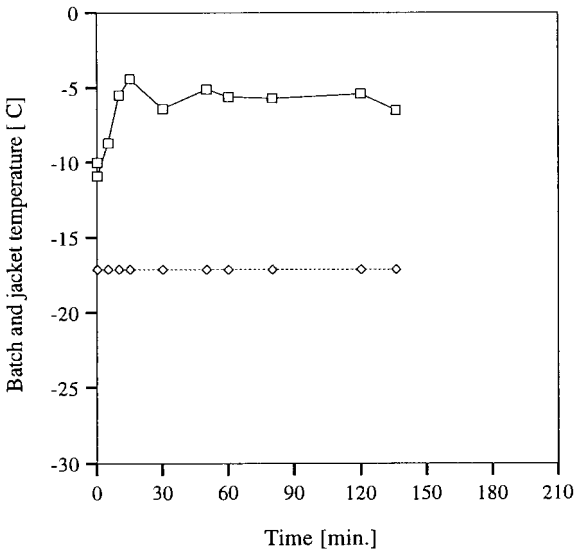

Figure 2. **Batch (□) and jacket (◇) temperature vs addition time of MeMgCl to 2 (batch A).**

the temperature was kept at ca. −10 °C. Although the total addition time of MeMgCl was shorter in the first batch (Figures 2 and 3), the reagent was added at a higher rate toward the end of the step in the second batch. Comparison of HPLC runs after completion of the Grignard step showed a decrease in the amount of primary alcohol **8** (Table 2).

Conclusions

To minimize formation of impurity **3**, the primary alcohol **8** that was formed by Mg-MPVO reaction pathway had to be reduced. The only variables to control the reaction were temperature and addition time. Chemical properties of the substrates favored Mg-MPVO reaction in competition with the Grignard addition. The solvent (THF) had the opposite effect. The decrease in the amount of **8** was achieved by reasonably fast (2−3 h) addition of MeMgCl solution in THF at low temperature (<−6 °C). As result, the second

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(21) The presence of ketone **4** in the reaction mixture and minimal formation of tertiary alcohol **9** can be explained by a reaction of the former with the base (chloromagnesium *sec*-alcoholate **7**-Mg or MeMgCl) to form an enolate. Cf. refs 11, 17b. In fact, a slow, dropwise addition of MeMgCl into **4** in THF produced extensive frothing, and **4** was recovered upon quenching. Ketone **4** can also be in a complex prior to hydrolysis. See ref 9b.

(22) These reactions appear to be rather rapid. Cf. ref 10.

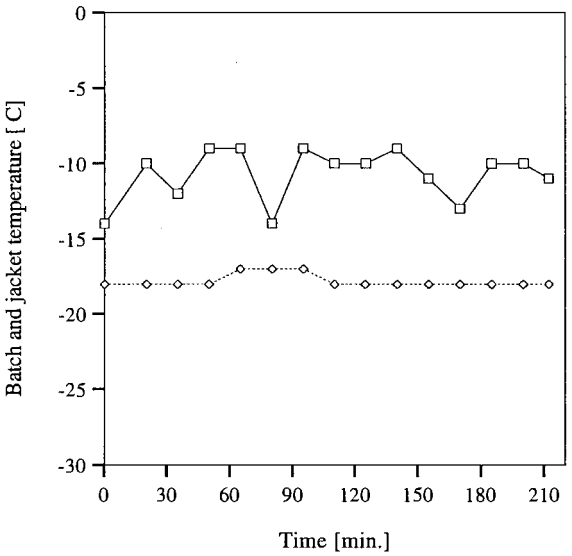

Figure 3. **Batch (□) and jacket (◇) temperature vs addition time of MeMgCl to 2 (batch B).**

Table 2. **Product distribution (HPLC area, %) in batches A and B after MeMgCl addition**

batch	**8**	**7**	**9**	**2 + 4**[a]
A	2.7	95.8	0	1.5
B	1.4	98.0	0.4	0.2

[a] Both **2** and **4** were inseparable under the HPLC conditions.

improved batch contained only 0.09% of impurity **3**, as compared to 0.50% in the first batch.

Experimental Section

All the reagents and solvents were used as purchased, except where indicated. ^{1}H NMR spectra were determined on a Bruker Avance DPX 300 (300.13 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR spectra were recorded at 75.47 MHz. Carbon chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ (77.09 ppm). IR spectra were obtained on a Mattson RS-1 FT-IR spectrometer and are uncalibrated. UV spectra were obtained on a Hewlett-Packard HP-8450A spectrophotometer as solutions in acetonitrile. Electron ionization mass (EI-MS) spectra were obtained on a Finnigan MAT 90 spectrometer. Flash column chromatography was carried out on J.T. Baker 40 μm silica gel using hexanes−EtOAc (2:1 v/v). HPLC scans were obtained on a Hitachi D-6000 instrument with a Partisil 5 μm, ODS-3, 4.6- × 250-mm column (Whatman); phosphate buffer pH 3.5−acetonitrile (3:2 v/v); flow 1.0 mL/min; wavelength 226 nm.

Aldehyde Oxime Carbamate 3. Purified **5** (4.4 g) underwent carbamoylation according to the literature procedure.[23] The aqueous solution was decanted, and the remaining oil was slurried in a toluene−heptane mixture. The resulting yellow solid was washed with heptane and dried in vacuo to give 1.7 g of a crude product. It was recrystallized from THF−heptane to give a light yellow solid (1.5 g, 27% yield; purity 96.5% by HPLC area).

^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 8.25 (s, 1H), 7.26 (s, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.35 (br s, 2H), 4.84 (m, 1H), 3.89 (s, 3H), 2.00−1.81 (m, 6H), 1.62 (m, 2H). ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 142.6, 139.5, 139.3, 134.1, 109.2, 108.8, 99.0, 97.7, 66.6, 42.1, 18.8, 10.2. UV: λ_{max} 210 nm (ϵ 67.5). IR (KBr): 3451, 3411 (NH_2), 1724 (C═O), 1261, 1016 (C−O), 954 (N−O) cm^{-1}. EI-MS: m/z (relative intensity) 278 (M^+), 277 ($M^+ - H$), 209, 167 (100), 149. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.53; N, 10.06. Found: C, 60.32; H, 6.64; N, 10.19.

Aldehyde oxime 5 was prepared according to the known procedure.[2b] Thus, the aldehyde **2** (8.8 g; 40 mmol) gave 9.9 g of a light yellow oil which solidified on standing to a waxy, cream-colored solid. The material was a mixture of the *E* and *Z* isomers. The two isomers separated on TLC (R_f *Z* = 0.22, *E* = 0.36), whereas HPLC scan showed only one peak with 99.7 area %, most likely the *E* isomer. Milligram quantities of each isomer were isolated by Prep LC (Waters LC 2000; PrepPak Porasil 15−20 μm, 125 Å; hexanes−EtOAc (5:1 v/v)) and the structures confirmed by NMR and MS. A solution of the *Z* isomer in chloroform-*d* was rescanned after 18 h, showing almost complete conversion to the *E* isomer.

^{1}H NMR: δ (*E*) 8.94 (br s, 1H), 8.08 (s, 1H), 7.21 (s, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 4.81 (m, 1H), 3.87 (s, 3H), 2.06−1.78 (m, 6H), 1.58 (m, 2H); (*Z*) 7.72 (s, 1H), 7.41 (dd, J = 8.4, 2.0 Hz, 1H), 7.27 (s, 1H), 6.89 (d, J = 8.5 Hz, 1H), 4.81 (m, 1H), 3.89 (s, 3H), 1.97−1.83 (m, 6H), 1.61 (m, 2H). ^{13}C NMR: δ (*E*) 148.3, 146.8, 144.6, 121.4, 118.0, 108.0, 77.1, 52.6, 29.3, 20.7. UV: λ_{max} 217 nm (ϵ 91.4). IR (KBr): 3475 (OH), 1625 (C═N), 948 (N−O) cm^{-1}. EI-MS: m/z (relative intensity) 235 (M^+), 167 (100), 152, 124. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.64; H, 7.45; N, 6.01. In support of the structure, oxime **5** was converted to its acetate.[24] Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.92; N, 5.05. Found: C, 65.02; H, 7.11; N, 5.09.

Secondary alcohol 7 was prepared according to the published procedure.[2b]

^{1}H NMR: δ 6.93 (d, J = 1.8 Hz, 1H), 6.88 (dd, J = 8.2, 1.8 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 4.80 (m, 2H), 3.84 (s, 3H), 1.99−1.80 (m, 6H), 1.61 (m, 2H), 1.48 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 149.2, 147.6, 138.5, 117.5, 112.3, 111.7, 80.3, 70.0, 56.0, 32.7, 25.0, 24.0.

Primary Alcohol 8. A solution of sodium borohydride (0.1 g; 3 mmol) in 20% sodium hydroxide (10 mL) was added dropwise into a stirred solution of **2** (1.1 g; 5 mmol) in 2-propanol (5 mL) in an ice bath. After the reaction was completed (TLC), the mixture was acidified with 2 M HCl and extracted with ether. The organic phase was washed with water and dried over $MgSO_4$. Filtration followed by evaporation gave **8** as an oil (0.9 g; 81% yield). An analytical sample was obtained using flash column chromatography (purity 98.1% by HPLC area).

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(24) Barbry, D.; Champagne, P. *Synth. Commun.* **1995**, *25*, 3503.

^{1}H NMR: δ 6.92 (s, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 4.80 (m, 1H), 4.61 (s, 2H), 3.84 (s, 3H), 2.13−1.78 (m, 6H), 1.61 (s, 2H). ^{13}C NMR: δ 149.4, 147.6, 133.6, 119.3, 114.0, 111.7, 80.3, 65.0, 56.0, 32.7, 24.0. IR (neat): 3391 (OH) cm^{-1}. EI-MS: *m*/*z* (relative intensity) 222 (M^+), 154 ($M^+ - C_5H_8$; 100). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.99; H, 8.12.

Tertiary Alcohol 9. To a solution of **4** (0.2 g; 1.0 mmol) in THF (4.5 mL) was added a solution of methylmagnesium chloride in THF (3 M; 3 mL; 9 mmol) in one portion from a syringe. The reaction was exothermic. It was allowed to stir at room temperature for 30 min (a single spot by TLC), quenched into water (30 mL) in a 250-mL Erlenmeyer flask, and extracted with ethyl acetate (70 mL). The organic phase was washed with water, separated, and dried over $MgSO_4$. Filtration followed by evaporation gave an oil which was passed through a small silica gel column. Evaporation of the eluent, followed by flash column chromatography, gave **9** (0.2 g; 83% yield; purity 99.0% by HPLC area).

^{1}H NMR: δ 7.08 (s, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.3 Hz, 1H), 4.80 (m, 1H), 3.84 (s, 3H), 2.04−1.78 (m, 6H), 1.62 (m, 2H), 1.57 (s, 6H). ^{13}C NMR: δ 148.8, 147.3, 141.9, 116.4, 112.2, 111.5, 80.5, 72.2, 56.1, 32.8, 31.7, 24.0. IR (neat): 3427 (OH) cm^{-1}. EI-MS: (relative intensity) *m*/*z*: 250 (M^+), 232 ($M^+ - H_2O$), 182 ($M^+ - C_5H_8$), 167 ($M^+ - C_5H_8 - CH_3$; 100), 164 ($M^+ - H_2O - C_5H_8$). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H 8.86. Found: C, 71.91; H 8.86.

Reactions of MeMgCl and 7-Mg with 2. The experiments were run on a 7−10 mmol scale. The analytical aliquots (10 μL) were quenched into the HPLC mobile phase (2 mL), homogenized with Vortex, filtered through Acrodisc CR PTFE (0.45 μm), and analyzed on a Hitachi D-6000 instrument.

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