A Simple Method for the Synthesis of Substituted Benzylic Ketones: Homologation of Aldehydes via the in Situ Generation of Aryldiazomethanes from Aromatic Aldehydes

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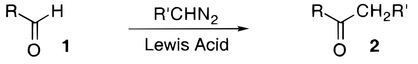
A general method for the homologation of aldehydes to benzylic ketones has been developed. Aryldiazomethanes were generated in situ in the presence of an aldehyde by simply heating the tosylhydrazones of aromatic aldehydes in the presence of a stoichiometric amount of base in polar protic solvents. The resulting polar protic solvent promoted homologation afforded benzylic ketones in moderate to excellent yields with a variety of aldehydes. Isolation of the tosylhydrazones was not necessary; they could be prepared in ethanol and carried through the sequence without isolation. This methodology allows easy access to a wide variety of substituted aryldiazomethanes that would be difficult, or even impossible, to prepare via conventional methods and circumvents the toxicity and stability problems associated with the isolation and/or handling solutions of aryldiazomethanes.

Introduction

The conversion of aldehydes to ketones can be accomplished by a variety of methods, the most common being a two-step process involving addition of a Grignard reagent to the aldehyde followed by oxidation to the ketone.[1] This conversion can also be accomplished in a single step by reaction of an aldehyde with a diazo compound in the presence of a Lewis acid or other activating agent (eq 1).[2] The relatively stable diazo compounds trimethylsilyldiazomethane[3] and ethyl diazoacetate[4] have both seen wide application in the one-step homologation of aldehydes to methyl ketones and β-ketoesters, respectively (eq 1). Aryldiazomethanes[5,6] were used by Anselme and co-workers for the one-step homologation of aldehydes **1** to benzylic ketones **2** (R′ = aryl).[7] These workers found that treatment of aryl and primary alkyl aldehydes with an aryldiazomethane in ether saturated with lithium bromide afforded good to excellent yields of benzyl ketones. Sterically demanding aldehydes, such as pivalaldehyde, failed to afford homologation products. We report here a general method for the in situ preparation of aryldiazomethanes that allows a one-step homologation of an aldehyde to a benzylic ketone and avoids isolation or handling solutions of the potentially toxic and explosive aryldiazomethanes.[5]



(eq 1)

To date, it has not been possible to carry out the synthesis of an aryl diazo compound and homologation to a benzylic ketone in the same reaction flask due to the incompatibility of the reaction conditions for the two steps: synthesis of the aryldiazo compound requires a protic solvent,[5,6] and the previously reported homologation reactions require aprotic solvents and anhydrous conditions.[7,8] For example, aryldiazomethanes are easily prepared by Bamford−Stevens reaction of the tosylhydrazones of aromatic aldehydes in ethylene glycol and other alcohol solvents[6] whereas Anselme's homologation with aryldiazomethanes is carried out in anhydrous ether.[7]

Results and Discussion

Bradley and co-workers have shown that methanol promotes the addition of diazomethane to aldehydes and ketones,[9] and it seemed reasonable that the reaction of phenyldiazomethane might also be facilitated by methanol. If this were the case, it seemed likely that methanol, or other alcohols, might serve a dual role as solvent for aryldiazomethane synthesis and promoter for the addition of the diazo compound to the aldehyde. In an effort

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[1] Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994.

[2] For leading references and reviews see: (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364−429. (b) Wulfman, D. S.; Linstrumelle, G.; Cooper, C. F. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Interscience: New York, 1978; p 821. (c) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725−4726. (e) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283−1290.

[3] (a) Aoyama, T. *Yakugaku Zasshi* (Journal of the Pharmaceutical Society of Japan) **1991**, *111*, 570−584. (b) Podlech, J. *J. Prakt. Chem./Chem.- Ztg.* **1998**, *340*, 679−682. (c) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619−4622. (d) Werner, R. M.; Shokek, O.; Davis, J. T. *J. Org. Chem.* **1997**, *62*, 8243−8246.

[4] (a) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260. (b) Holmquist, C. R.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1131−1134. (c) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5055−5058.

[5] For methods to prepare aryldiazomethanes see: (a) Creary, X. *J. Am. Chem. Soc.* **1980**, *102*, 1611−1618. (b) Creary, X. *Org. Synth.* **1985**, *64*, 207−216. (c) Overberger, C. G.; Anselme, J.-P. *J. Org. Chem.* **1963**, *28*, 592−593. (d) Kaufman, G. M.; Smith, J. A.; VanderStouw, G. G.; Shechter, H. *J. Am. Chem. Soc.* **1965**, *87*, 935−937.

[6] Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735−4740. This reference contains a study following the conversion of benzaldehyde tosylhydrazone to phenyldiazomethane in ethanol and monitors its concentration at periodic intervals over 24 h.

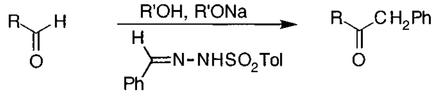
[7] Loeschorn, C. A.; Nakajima, M.; McCloskey, P.; Anselme, J.-P. *J. Org. Chem.* **1983**, *48*, 4407−4410.

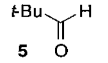
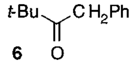
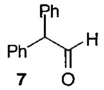
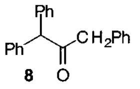
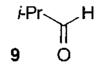
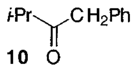
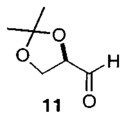
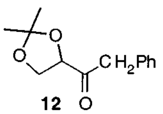
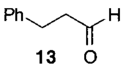
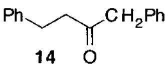
[8] Mahmood, S. J.; Saha, A. K.; Hossain, M. M. *Tetrahedron* **1998**, *54*, 349−358.

[9] Bradley, J. N.; Cowell, G. W.; Ledwith, A. *J. Chem. Soc.* **1964**, 4334−4339.

10.1021/jo000446y CCC: $19.00

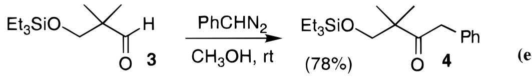
Table 1. Synthesis of Benzyl Ketones



Entry	Aldehyde	Cond.[a]	Benzyl Ketone	Yield
1	 5	72 h, 50 °C EtOH[b]	 6	90%
2	 7	4 h, 65 °C MeOH	 8	84%
3	 9	4 h, 65 °C MeOH	 10	53%
4		24 h, 50 °C EtOH		56%
5	 11	0.75 h, 65 °C MeOH	 12	66%
6	 13	6 h, 60 °C MeOH	 14	46%
7		6 h, 60 °C EtOH		44%

[a] 2 equiv of hydrazone were used in reactions run in EtOH and 3 equiv were used for reactions in MeOH. [b] In MeOH the reaction mixture contained byproducts that made purification difficult.

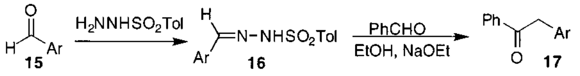
to test this notion, aldehyde **3**[10] was treated with phenyldiazomethane (2 equiv) in methanol (rt, 2 days) to afford benzyl ketone **4** in 78% yield after flash chromatography (eq 2). This result provides an opportunity for realizing a one-pot aldehyde to ketone homologation reaction.

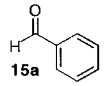
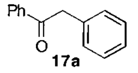
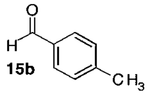
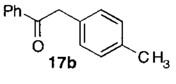
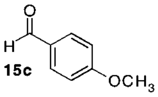
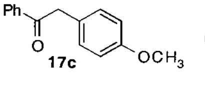
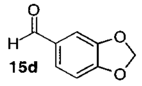
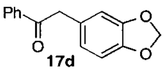
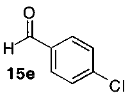
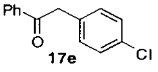


(eq 2)

The one-pot homologation of a series of readily available aldehydes with phenyldiazomethane is summarized in Table 1. Heating a solution of the aldehyde and benzaldehyde tosylhydrazone (2 equiv) in methanol or ethanol solvent with 2 equiv of the appropriate alkoxide resulted in the slow generation of phenyldiazomethane.[6] The reaction mixture was stirred until the pink color of the phenyldiazomethane had faded, indicating its complete consumption by reaction with the alcohol solvent and thereby avoiding the potential hazard of isolating the diazo compound. Concentration, aqueous workup, and flash chromatography afforded the benzylic ketones in the yields shown. Reactions carried out in methanol required 3 equiv of hydrazone for the complete reaction of aldehyde, whereas those in ethanol required only 2 equiv of hydrazone. The reason for the different stoichiometry appears to be due to the faster side reaction of phenyldiazomethane with methanol over ethanol.[11] All other factors being equal, ethanol is the solvent of choice; purification is easier due to fewer hydrazone derived byproducts.

Table 2. Reactions of Substituted Aryldiazomethanes



Entry	Aldehyde 15	Cond.	Ketone 17	Yield[a]
1	 15a	48 h 55 °C	 17a	42%[b]
2	 15b	48 h 50 °C	 17b	88%
3	 15c	48 h 50 °C	 17c	63%
4	 15d	48 h 50 °C	 17d	52%[c]
5	 15e	40 h 60 °C	 17e	81%

[a] Yield refers to the **16** to **17** transformation and is based on benzaldehyde with 2 equiv of hydrazone. [b] Ketone **8** was isolated in 25% yield. [c] The hydrazone was prepared in situ and the yield is for **15d** to **17d**.

The examples in Table 1 show that the substituents α to the aldehyde have a direct effect on the yield of the homologation reaction. The more bulky the substituent, the higher the yield of benzyl ketone. It is worth noting that the reaction conditions are also compatible with an acetonide (Table 1, entry 5); however, racemization of the stereogenic center did occur. This method is complementary with the LiBr-promoted reactions. Anselme was unable to isolate benzyl ketone products when aldehydes **5**, **7**, and **9** were reacted with phenyldiazomethane,[7] whereas we obtain good to excellent yields of benzyl ketones from these aldehydes. Our yields are lowest with nonbranched aliphatic aldehyde **13**, and these substrates afforded the highest yields in the LiBr-promoted reactions.[7] Despite the decrease in yield for unhindered aldehydes, our procedure provides considerable advantage over existing methodology due to the simplicity and safety of the reaction conditions.

Substituted aryldiazo compounds can be prepared in situ and reacted with an aldehyde using this methodology. Table 2 shows several examples where readily available aldehydes **15** were converted to the corresponding tosylhydrazones **16** and then reacted with benzaldehyde to afford benzylic ketones **17**. In the case of **15a**,

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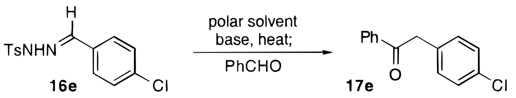
[10] Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **1999**, *64*, 8754–8757.

[11] For discussions of the stability of diazo compounds to protic solvents: (a) Finneman, J. I.; Fishbein, J. C. *J. Org. Chem.* **1994**, *59*, 6251–6256. (b) Finneman, J. I.; Fishbein, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 4228–4239. See also ref 6.

Table 3. Effect of Solvent on Homologation



entry	equiv of **16**	cond.	solvent	base	yield of **17**, %
1	3	28 h, 50 °C	MeOH	NaOMe	77
2	3	0.5 h, 80 °C	$(HOCH_2)_2$	NaOR	71
3	3	1 h, 90 °C	H_2O	NaOH[a]	76
4	2	21 h, 60 °C	95% EtOH	NaOH[b]	79
5	2	4 h, 60 °C	formamide	NaOH[b]	21
6	3	6 d, 60 °C	DMSO	NaOH[b]	<3

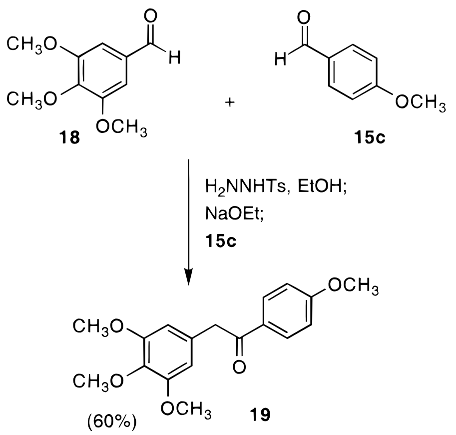
[a] 1 M aqueous solution. [b] Pellets.

the product **17a** reacted with phenyldiazomethane to afford **8** in 25% yield. This is the only example where products derived from subsequent reaction of the initial homologation product were observed. The preparation of the acetal containing aryldiazomethane in entry 4 was problematic due to difficulties in isolating tosylhydrazone **16d**. To circumvent this problem, the corresponding aldehyde, **15d**, was reacted with tosylhydrazide in ethanol to afford the hydrazone, and then sodium ethoxide (2 equiv) and benzaldehyde were added. Heating this solution for 2 days at 55 °C afforded a 52% yield of ketone **17d**.

In an attempt to investigate the range of solvents compatible with the reaction, benzaldehyde was homologated with *p*-chlorobenzaldehyde tosylhydrazone using a variety of polar protic solvents (Table 3). As can be seen, the yields of benzylic ketone **17e** range from 71% to 79% when polar protic solvents are used. Polar aprotic solvents formamide and DMSO afforded **17e** in 21% and <3% yield, respectively. Thus, the reaction appears to require a polar protic solvent for good yields of homologation products.

This new methodology is versatile and convenient. For example, hydrazone **16e** (Table 3, entry 3) was simply dissolved in 1 M aqueous NaOH and then heated with benzaldehyde. Aqueous workup and flash chromatography afforded **17e** in 76% yield. As outlined in entry 4, neat NaOH was added to the hydrazone in 95% ethanol and then heated with benzaldehyde to afford ketone **17e** in a 79% yield after aqueous workup and flash chromatography.

The in situ formation of tosylhydrazones from aromatic aldehydes followed by base-promoted Bamford–Stevens reaction[6] was already used to advantage in the synthesis of **17d** from **15d** and benzaldehyde (Table 2, entry 4). This methodology provides the opportunity to utilize aryldiazomethanes containing electron-releasing substituents that would be difficult, or even impossible,[11,12] to prepare via conventional methods.[5,6] To illustrate the generality of this method, aldehyde **18** was reacted with tosylhydrazide in ethanol to effect hydrazone formation (eq 3). Addition of sodium ethoxide followed by *p*-methoxybenzaldehyde, **15c**, and heating for 39 h afforded ketone **19** in 60% isolated yield.



Conclusion

We have developed a general method for the homologation of an aldehyde with an arylaldehyde to afford moderate to excellent yields of benzylic ketones. The need to isolate and/or handle solutions of diazo compounds is eliminated and excess reagent is destroyed by reaction with solvent prior to workup. Efforts to exploit this methodology in the synthesis of natural products is currently under study.

Experimental Section

General Information. The starting aldehydes were purchased from Aldrich or Acros. Tosylhydrazones were prepared according to literature procedures.[6] All capillary GCs were run on a 25 m HP 1 (methyl silicone column) with a flame ionization detector. Unless stated otherwise, the following standard parameters were used: initial temperature = 40 °C; final temperature = 170 °C; heating rate = 10 °C per minute; injector temperature = 150 °C; detector temperature = 250 °C.

3,3-Dimethyl-1-phenyl-4-(triethylsilyl)oxy-2-butanone (4). Freshly distilled phenyldiazomethane (0.46 mmol, 54 mg, **Caution: Diazo compounds are toxic and potentially explosive**) was added to aldehyde **3** (0.23 mmol, 50 mg) in anhydrous methanol (0.1 M). The reaction was protected from light and stirred at room temperature for 48 h at which time the red color of the phenyldiazomethane had disappeared. The solvent was removed in vacuo, and the resulting oil was diluted with H_2O (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford 81 mg of a light yellow oil. Flash chromatography (silica gel, hexanes/ethyl acetate) afforded the known[10] benzyl ketone **4** (54 mg, 78%) as a colorless oil.

General Procedure for the Preparation of Ketones 6, 8, 10, 12, 14, 17a–c, and 17e. A 2 M solution of the sodium alkoxide or sodium hydroxide (see Tables 1–3 for details; sodium alkoxides were freshly prepared from sodium (92 mg, 4.0 mmol) and the alcohol (20 mL)) was added to benzaldehyde tosylhydrazone or hydrazones **16** (4.0 mmol) in alcohol solvent (20 mL). The resulting solution was protected from light, the appropriate aldehyde (2.0 mmol) was added, and the reaction mixture was heated for the time indicated in each experimental (the light red color of the aryldiazomethane had disappeared). In the case of reactions run in methanol and ethanol, the solvent was removed in vacuo. The residue was diluted with H_2O (100 mL) and $CHCl_3$, (50 mL). The aqueous layer was extracted with $CHCl_3$, (2 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford crude products. Flash chromatography (silica gel, hexanes/ethyl acetate) afforded the product ketones in the yields indicated.

3,3-Dimethyl-1-phenyl-2-butanone (6). According to the general procedure the reaction mixture was heated for 72 h at 50 °C to afford the known[13] ketone **6** as a light yellow oil in 90% yield: purity by GC = 96.7% (t_R = 22.40 min; heating rate = 5 °C per min; detector temperature = 200 °C).

1,1,3-Triphenyl-2-propanone (8). According to the general procedure the reaction mixture was heated for 4 h at 65

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(12) Closs, G. L.; Moss, R. A. *J. Am. Chem. Soc.* **1964**, *86*, 4042–4053.

°C to afford the known[14] ketone **8** as a white solid in 84% yield; mp 73−74 °C, (no lit. melting point[14]); purity by GC = 98.4% (t_R = 32.29 min; final temperature = 220 °C, injector temperature = 220 °C).

3-Methyl-1-phenyl-2-butanone (10). According to the general procedure the reaction mixture was heated for 24 h at 50 °C to afford the known[15] ketone **10** as a clear oil in 56% yield: purity by GC = 98.2% (t_R = 20.75 min; heating rate = 5 °C per min; detector temperature = 200 °C).

3,4-*O*-Isopropylidene-1-phenyl-2-butanone (12). According to the general procedure the reaction mixture was heated for 0.75 h at 50 °C to afford ketone **12** as a clear oil in 66% yield. Chiral shift study using Eu(hfc)$_3$ showed the product to be racemic: purity by GC = 88.9% (t_R = 21.30 min; injector temperature = 170 °C, detector temperature = 225 °C); ^{1}H NMR (300 MHz, CDCl$_3$)δ 7.29−7.12 (m, 5H), 4.45 (dd, J = 7.7, 5.6 Hz, 1H), 4.09 (dd, J = 8.7, 7.7 Hz, 1H), 3.95 (dd, J = 8.7, 5.6 Hz, 1H), 3.85 (ABq, J = 15.4 Hz, $\Delta\nu$ = 26.1 Hz, 2H), 1.44 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$)δ 207.7, 133.2, 129.6, 128.6, 127.0, 111.0, 79.9, 66.4, 45.4, 26.0, 25.0; IR (neat) 2988, 1721, 1373, 1151, 1066 cm^{-1}; MS (CI, NH$_3$) m/z 221 (100, MH$^+$), 101 (23); HRMS calcd for $C_{13}H_{17}O_3$ (M+H) 221.1177, found 221.1170.

1,4-Diphenyl-2-butanone (14). Heated for 6 h at 60 °C to afford the known[16] ketone **14** as a white solid 44% yield: mp 41−43 °C, (lit.[16b] 41−42 °C); purity by GC = 99.9% (t_R = 21.57 min; final temperature = 220 °C, injector temperature = 220 °C).

2-Phenylacetophenone (17a). According to the general procedure the reaction mixture was heated for 48 h at 55 °C to afford the known[7,17] ketone **17a** as a white needles (ethanol) in 42% yield: mp 54−55 °C, (lit.[7] 55−56 °C); purity by GC = 99.9% (t_R = 21.12 min; final temperature = 220 °C, injector temperature = 170 °C, detector temperature = 250 °C).

2-(4-Methylphenyl)acetophenone (17b). According to the general procedure the reaction mixture was heated for 48 h at 50 °C to afford the known[18] ketone **17b** as clear plates in 88% yield: mp 95−96 °C, (lit.[18] 97.5−99 °C); purity by GC = 99.9% (t_R = 37.46 min; detector temperature = 200 °C).

2-(4-Methoxyphenyl)acetophenone (17c). According to the general procedure the reaction mixture was heated for 48 h at 50 °C to afford the known[18] ketone **17c** as clear plates in 63% yield: mp 93−94 °C, (lit.[18] 95.5−96 °C); purity by GC = 98.4% (t_R = 27.34 min; detector temperature = 200 °C).

2-(4-Chlorophenyl)acetophenone (17e). According to the general procedure the reaction mixture was heated for 40 h at 60 °C to afford the known[18] ketone **17e** as clear plates in 81% yield: mp 129−130 °C, (lit.[18] 137.5−139 °C); purity by GC = 95.9% (t_R = 25.72 min; final temperature = 200 °C).

General Procedure for the Preparation of Ketones 17d and 19. The aldehyde (**18** or **15d**, 4.0 mmol) was added to toluenesulfonhydrazide (0.745 g, 4.0 mmol) in absol ethanol (20 mL), and the resulting solution was stirred at room temperature for 40 min. A solution of 2 M sodium ethoxide (20 mL, freshly prepared from sodium and ethanol) was then added, the resulting solution was heated to 55 °C, and aldehyde **15a** or **15c** (2.0 mmol) was added. The reaction was protected from light and stirred at 55 °C for the time indicated in each experimental (the light red color of the aryldiazomethane had disappeared). Workup and chromatography as noted above afforded products **17d** and **19** in the yields indicated.

2-Piperonylacetophenone (17d). According to the general procedure the reaction mixture was heated for 48 h at 50 °C to afford the known[19] ketone **17d** as a clear oil in 52% yield: purity by GC = 96.1% (t_R = 26.38 min; final temperature = 220 °C, injector temperature = 185 °C).

2-(2,3,4-Trimethoxyphenyl)-4-methoxyacetophenone (19). According to the general procedure the reaction mixture was heated for 39 h at 50 °C; white solid, mp 80−85 °C; 60% yield; purity by GC = 99.9% (t_R = 24.43 min; heating rate = 20 °C per min; final temperature = 250 °C, injector temperature = 220 °C); ^{1}H NMR (300 MHz, CDCl$_3$)δ 8.00 (dm, J = 9.2 Hz, 2H), 6.93 (dm, J = 8.7 Hz, 2H), 6.47 (s, 2H), 4.16 (s, 2H), 3.86 (s, 3H), 3.82 (s, 6H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$)δ 196.1, 163.6, 153.3, 136.8, 130.9, 130.5, 129.6, 113.8, 106.4, 60.8, 56.1, 55.4, 45.4; IR (KBr) 2935, 2834, 1675, 1596, 1509, 1122 cm^{-1}; MS (EI, 70 eV) m/z 316(14, M$^+$), 181 (15), 135 (100); HRMS calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1301.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for compounds **6**, **8**, **10**, **12**, **14**, **17a**−**e**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Compound **17a**, deoxybenzoin, is commercially available from Aldrich.

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