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Synthesis of 2-Alkenyl-3-(alkoxycarbonyl)furans Based on Feist−Benary Cyclocondensation of (2,4-Dioxobutylidene)phosphoranes with α-Haloketones and α-Chloracetaldehyde

Gerson Mross,[†] Edith Holtz,[‡] and Peter Langer*[,†,§]

Institut für Chemie, Universität Rostock, Albert-Einstein-Strasse 3a, 18059 Rostock, Germany, Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany, and Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany

peter.langer@uni-rostock.de.

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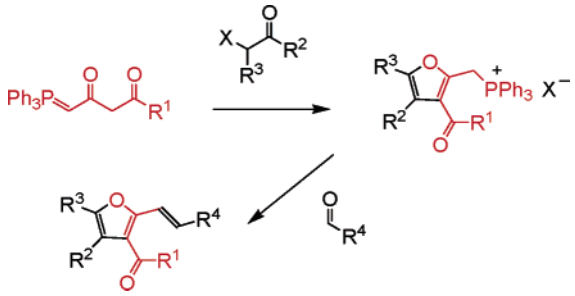

3-Acyl-2-alkenylfurans were prepared by "Feist−Benary cyclocondensation" of (2,4-dioxobutylidene)-phosphoranes with chloracetaldehyde and α-haloketones and subsequent Wittig reactions.

Functionalized furans are present in a great variety of pharmacologically relevant natural products.[1,2] 3-Acylfurans, such as (−)-myodesmone and 7-hydroxymyoporone, constitute a large and important subgroup of naturally occurring furans.[3] Likewise, 2-alkenylfurans are widespread in nature.[4] In addition, they are of considerable pharmacological relevance and have been used as synthetic building blocks. Although a number of synthetic approaches to furans have been reported,[1,2] the development of new and more efficient strategies is of ongoing interest. New synthetic approaches to furans should allow a facile assembly of substitution patterns which are not readily available by other methods. In recent years, we have reported a number of synthetic approaches to (furan-2-yl)acetates based on cyclization reactions of 1,3-dicarbonyl dianions or 1,3-bis-(silyl enol ethers) with 1,2-dielectrophiles.[5] The Feist−Benary cyclocondensation of 1,3-dicarbonyl compounds with haloketones represents a classical method for the synthesis of furans containing an ester or ketone substituent at carbon C-3.[1] Recently, we reported[6] the synthesis of 2-alkenyl-3-(alkoxycarbonyl)furans by Feist−Benary cyclocondensation of (2,4-dioxobutylidene)phosphoranes[7] with chloracetaldehyde to give (furylmethyl)phosphonium chlorides[8] and subsequent Wittig reactions. Herein, we report full details of this methodology. With respect to our preliminary communication,[6] the preparative scope was significantly extended. An improved procedure was developed which allows, for the first time, the employment of

[†] Institut für Chemie, Universität Rostock. Fax: +381 4986412.

[‡] Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen.

[§] Leibniz-Institut für Katalyse e. V. an der Universität Rostock.

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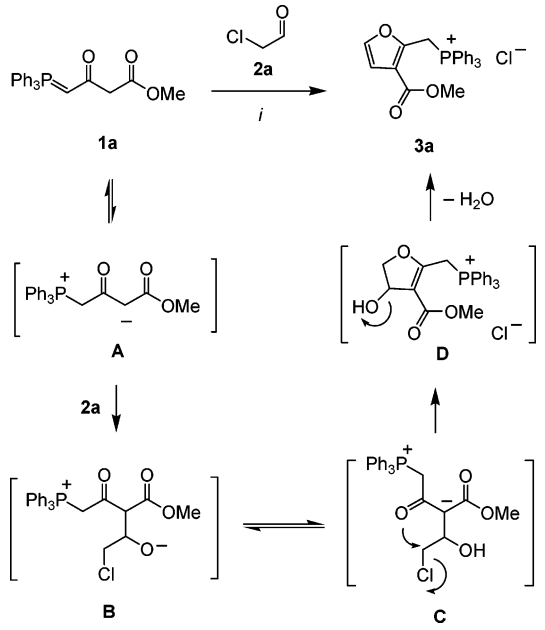
α-haloketones as starting materials and the synthesis of a great variety of novel 3-acyl-2-alkenylfurans. Notably, 3-acyl-2-alkenylfurans have been shown to be of considerable pharmacological relevance.[9]

Results and Discussion

The reaction of chloracetaldehyde (**2**) with (2,4-dioxobutylidene)phosphorane (**1a**), prepared by reaction of triphenylphosphane with ethyl 4-chloroacetoacetate, afforded the (2-furylmethyl)phosphonium chloride **3a** (Scheme 1). The formation of **3a** can be explained by tautomerization of **1a** to give intermediate **A**, attack of the central carbon atom of the latter onto the aldehyde (intermediate **B**), 1,3-prototropic shift (intermediate **C**), cyclization by attack of the carbonyl oxygen atom onto the chloride (intermediate **D**), and subsequent elimination of water.

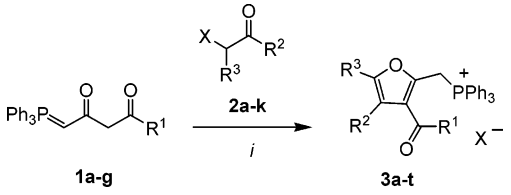
The cyclization of **2a** with phosphoranes **1b**−**g** afforded the alkoxycarbonyl-, carbamoyl-, and benzoyl-substituted (2-furyl)-methylphosphonium chlorides **3b**−**g** (Scheme 2, Table 1). The

SCHEME 1. Cyclization of (2,4-Dioxobutylidene)phosphorane 1a with Chloracetaldehyde (2a)[a]



[a] Key for step i: CH_2Cl_2, reflux 24 h.

SCHEME 2. Cyclization of (2,4-Dioxobutylidene)phosphoranes 1a−g with α-Haloketones and Aldehydes 2a−k[a]



[a] Key for step i: procedure A: CH_2Cl_2, reflux 24 h; procedure B: neat, 80 °C, 1 h; procedure C: neat, 80 °C, 1 h, 10^{-2} bar.

reactions of ester-derived phosphoranes **1a**−**c** proceeded in good yield. During the optimization, it proved to be important to carry out the reaction in the absence of base and under reflux conditions (procedure A, CH_2Cl_2, 24 h). No product could be isolated in the reaction of **1c** with **2a** when NaO*i*Pr/*i*PrOH or pyridine was employed which might be explained by nucleophilic attack of the base onto **2a**. The water had to be removed from the commercially available aqueous solution (45%) of **2a**. The protocol for purification of the phosphonium salt (silica gel chromatography; eluents, acetone and then MeOH) also played an important role (Table 1). The synthesis of **3c** was successfully scaled up from 1.1 to 11.0 mmol (Table 2). A change of the concentration of **1c** (0.02 versus 0.05 M) had no major influence on the yield.

Relatively low yields were obtained for benzoylacetone and ketoamide derived phosphoranes **1d**−**g** (Scheme 2). The low yields can be explained by the reduced acidity of the ketoamides (due to steric reasons) which results in a smaller amount of intermediate **A** present in the equilibrium. This assumption is supported by the fact that, in the case of the synthesis **3e**, the open-chained side-product **3e′** was isolated. The yields could not be improved by extension of the reaction time. However, the yields could be successfully improved by employment of

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TABLE 1. Products and Yields

3	R^1	R^2	R^3	X	% 3[a]	procedure[c]
a	OMe	H	H	Cl	43	A[d,g]
b	OEt	H	H	Cl	41	A[d,g]
c	O*i*Pr	H	H	Cl	27	A[d]
c	O*i*Pr	H	H	Cl	72	A[e]
d	NH_2	H	H	Cl	71[b]	B
e	$N(CH_2)_4$	H	H	Cl	37	A[e,f]
f	$N(CH_2)_5$	H	H	Cl	53	B
g	Ph	H	H	Cl	50	B
h	OMe	Me	H	Cl	52[b]	B
i	OEt	Me	H	Cl	49	B
j	O*i*Pr	Me	H	Cl	56	B
k	Ph	Me	H	Cl	43	B
l	OEt	CH_2Cl	H	Cl	35	A[g]
m	OEt	*t*Bu	H	Br	75	C
n	OEt	CH_2CO_2Et	H	Cl	63	C
o	OEt	Ph	H	Br	53	A[g]
p	OEt	Ph	Ph	Br	46	C
q	OEt	4-MeC_6H_4	H	Br	80	C
r	OEt	4-BrC_6H_4	H	Cl	71	C
s	OEt	4-$(O_2N)C_6H_4$	H	Br	80	C
t	OEt	4-ClC_6H_4	H	Br	52	C

[a] Isolated yields. [b] Unstable products. [c] Procedure A: CH_2Cl_2, reflux, 24 h. Procedure B: neat, 80 °C, 1 h. Procedure C: neat, 80 °C, 1 h, 10^{-2} bar. [d] Workup: washing of the crude product with acetone. [e] Workup: flash chromatography (silica gel; acetone and then MeOH). [f] In addition, **3e′** was isolated in 32% yield. [g] Experiments using procedures B or C have not been carried out.

TABLE 2. Scale-Up of the Synthesis of 3c

entry	**1c** (mmol)	**c** (mol/L)	yield (%)[a]
1	1.1	0.02	72
2	5.1	0.05	65
3	11.0	0.05	69

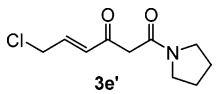
[a] Isolated yields.

TABLE 3. Optimization of the Synthesis of 3d,f,g

3	R^1	%[a,b]	%[a,c]	%[a,d]
g	Ph	28	33	50
d	NH_2	10	47	71
f	$N(CH_2)_5$	22	35	53

[a] Isolated yields. [b] Conditions: CH_2Cl_2, 40 °C, 24 h (procedure A). [c] Conditions: $(CH_2Cl)_2$, 60 °C, 48 h. [d] Conditions: neat, 80 °C, 1 h (procedure B).

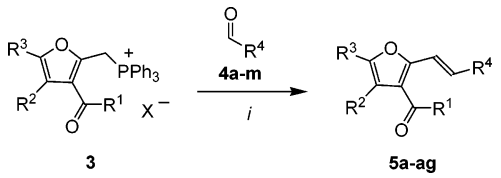
dichloroethane rather than dichloromethane as the solvent which allows an increase of the reaction temperature from 40 to 60 °C (Table 3). The best yields were obtained when the reactions were carried out at 80 °C without any solvent (procedure B). Notably, the application of this procedure allowed one to significantly shorten the reaction time to only 1 h.



3e'

The application of procedure A to the reaction of (2,4-dioxobutylidene)phosphoranes with α-haloketones gave unsatisfactory results (low conversion, decomposition). Eventually, optimal yields were obtained when the transformations were carried out following procedure B (vide supra) or procedure C (with repeated removal of water at 10^{-2} bar). Procedure C was applied for all cyclizations of nonvolatile α-haloketones and

SCHEME 3. Synthesis of Furans 5a−ag[a]



3 **5a-ag**

[a] Key for step i: (1) *n*BuLi, THF, 0 °C, 0.5 h; (2) **4**, THF, 0 °C, 0.5 h and then 20 °C, 4−72 h.

allowed the removal of water during the reaction. In case of solid starting materials, the melting was stirred at 80 °C. The most important factors responsible for the success of procedures B and C are presumably the reaction temperature of 80 °C and the high concentration of the starting materials (neat). The reaction of **1a**−**c**,**g** with 2-chloroacetone (**2b**) afforded the methyl-substituted (2-furyl)methylphosphonium chlorides **3h**−**k**. The cyclocondensation of **1b** with 1,3-dichloroacetone (**2c**), 1-bromo-3,3-dimethylbutan-2-one (**2d**), and ethyl 4-chloroacetoacetate (**2e**) afforded the corresponding (2-furyl)methylphosphonium chlorides **3l**−**n**. The aryl-substituted (2-furyl)-methylphosphonium halides **3o**−**t** were prepared by cyclization of **1b** with phenacyl bromide (**2f**), desyl bromide (**2g**), 4-(bromoacetyl)toluene (**2h**), 4-(chloroacetyl)-1-bromobenzene (**2i**), 4-(bromoacetyl)-1-nitrobenzene (**2j**), and 4-(bromoacetyl)-1-chlorobenzene (**2k**).

The (2-furyl)methylphosphonium salts were formed in moderate to very good yields. The lowest yields were obtained for difuncational 1,3-dichloroacetone and for reactions of amide-derived phosphoranes (vide supra). The best yields were obtained for reactions of phenacyl halides. There was no significant difference between phenacyl chlorides and bromides.

The Wittig reaction of (2-furyl)methylphosphonium halides **3** with various aldehydes was next studied (Scheme 3, Table 4). The reaction of **3c** with various aliphatic and aromatic aldehydes (**4a**−**l**) afforded the 2-alkenyl-3-(isopropoxycarbonyl)furans **5a**−**l** in moderate to good yields. The reaction of **3g** with butan-1-al and benzaldehyde afforded the furans **5m**,**n**, respectively. Furan **5o** was prepared from **3d**, albeit, in low yield. The reaction of **3h**−**k** with butan-1-al and benzaldehyde gave the furans **5p**−**t**. The furans **5u**,**v** were prepared by reaction of (2-furyl)methylphosphonium bromide **3m** with butan-1-al and benzaldehyde, respectively. The reaction of **3l** with butan-1-al and 4-methoxybenzaldehyde gave the 3-acyl-2-alkenyl-4-(chloromethyl)furans **5w**,**x**, respectively. The diesters **5y**,**z** were prepared from phosphonium salt **3n**. Wittig reactions of aryl-substituted (2-furyl)methylphosphonium halides **3o**−**t** afforded the 4-aryl-2-vinylfurans **5aa**−**ag**.

Optimization studies showed that the best yields were obtained when *n*BuLi/THF was employed (reaction time 0.5 h, 0 °C). The yield of **5e** dramatically decreased (to 15%) when NaOEt/EtOH or NaO*i*Pr/*i*PrOH were used. Most of the Wittig reactions of (2-furyl)methylphosphonium salts with aldehydes proceeded in good yields. The products were formed with good to excellent *E*-diastereoselectivity which can be explained by the presence of lithium chloride in the reaction mixture ("salt conditions"). Product **5c** was isolated in low yield, presumably due to conjugate addition of the phosphorane to crotonaldehyde. The yields of **5o** and **5af** were low, due to side reactions of *n*BuLi with the amino and the nitro group, respectively. The yield of **5o** could be improved to 30% by use of triethylamine rather than *n*BuLi. The low yields of **5t**,**u**,**aa** remain unclear at

TABLE 4. Products and Yields

5	R^1	R^2	R^3	R^4	*E*/*Z*	% (5)[a]
a	O*i*Pr	H	H	Me	4:1	62
b	O*i*Pr	H	H	Et	6:1	62
c	O*i*Pr	H	H		10:1	29
d	O*i*Pr	H	H		10:1	61
e	O*i*Pr	H	H	Ph	>98:2	67
f	O*i*Pr	H	H	3-MeC_6H_4	>98:2	53
g	O*i*Pr	H	H	4-$(MeO)C_6H_4$	>98:2	66
h	O*i*Pr	H	H	3,4-$(MeO)_2C_6H_3$	>98:2	73
i	O*i*Pr	H	H	4-$(Me_2N)C_6H_4$	>98:2	54
j	O*i*Pr	H	H	3-ClC_6H_4	10:1	54
k	O*i*Pr	H	H	3-$(O_2N)C_6H_4$	12:1	69
l	O*i*Pr	H	H	3-Pyridyl	10:1	74
m	Ph	H	H	*n*Pr	3:1	12
n	Ph	H	H	Ph	>98:2	60
o	NH_2	H	H	Ph	>98:2	24[b]
p	OMe	Me	H	*n*Pr	4:1	60
q	OEt	Me	H	Ph	>98:2	61
r	OEt	Me	H	*n*Pr	4:1	70
s	O*i*Pr	Me	H	*n*Pr	4:1	33
t	Ph	Me	H	*n*Pr	3:1	16[b]
u	OEt	*t*Bu	H	*n*Pr	6:1	5
v	OEt	*t*Bu	H	Ph	>98:2	64
w	OEt	CH_2Cl	H	*n*Pr	3:1	49
x	OEt	CH_2Cl	H	4-$(MeO)C_6H_4$	>98:2	62
y	OEt	CH_2CO_2Et	H	*n*Pr	4:1	45
z	OEt	CH_2CO_2Et	H	Ph	>98:2	41
aa	OEt	Ph	H	*n*Pr	3:1	30[b]
ab	OEt	Ph	Ph	*n*Pr	3:1	39
ac	OEt	Ph	Ph	Ph	>98:2	28
ad	OEt	4-MeC_6H_4	H	Ph	>98:2	42
ae	OEt	4-BrC_6H_4	H	Ph	>98:2	43
af	OEt	4-$(O_2N)C_6H_4$	H	Ph	>98:2	12
ag	OEt	4-ClC_6H_4	H	Ph	>98:2	36[b]

[a] Isolated yields. [b] Unstable products.

present. In fact, some products tend to be unstable during chromatographic purification. The Wittig reactions of aromatic aldehydes generally proceeded with better *E*-diastereoselectivity than those of aliphatic aldehydes which might be explained by steric reasons.

In conclusion, a variety of 3-acyl-2-alkenylfurans were prepared by Feist−Benary cyclocondensation of (2,4-dioxobutylidene)phosphoranes with chloracetaldehyde or α-haloketones and subsequent *E*-diastereoselective Wittig reactions.

Experimental Section

General Comments. All solvents were dried by standard methods, and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60−200 mesh) was used. Melting points are uncorrected.

General Procedure for the Synthesis of Phosphonium Halides 3. Procedure A. To a CH_2Cl_2 solution (20 mL) of chloracetaldehyde (45%, aqueous solution) was added $MgSO_4$. The solution was filtered, and the $MgSO_4$ was washed with CH_2Cl_2. The filtrate (50 mL) was added to phosphorane **1**, and the solution was refluxed for 24 h. The solvent was removed in vacuo. For **3a**,**b**, the residue was washed with acetone. For **3c**,**e**, the residue was purified by column chromatography (silica gel; acetone and then MeOH, i.d. = 2.0 cm).

Procedure B. To chloracetaldehyde (55%, aqueous solution) was added $MgSO_4$. The mixture was filtered to give neat chloracetaldehyde. To neat chloracetaldehyde or α-chloroacetone was added phosphorane **1**, and the mixture was vigorously stirred at 80 °C for 1 h. After being cooled to room temperature, the mixture was dissolved in CH_2Cl_2 (10 mL), and the solution was poured into hexane (500 mL). The oil layer was separated from hexane and was subsequently dissolved in CH_2Cl_2 (5 mL). The solution was filtered, and the solvent of the filtrate was removed in vacuo to give the (furylmethyl)phosphonium chloride **3**.

Procedure C. The neat anhydrous haloketone **2** and phosphorane **1** were vigorously stirred at 80 °C for 1 h. The reaction vessel was repeatedly evacuated (10^{-2} bar). After being cooled to room temperature, the mixture was dissolved in CH_2Cl_2 (10 mL), and the solution was poured into hexane (500 mL). The oil layer was separated from hexane and was subsequently dissolved in CH_2Cl_2 (5 mL). The solution was filtered, and the solvent of the filtrate was removed in vacuo to give the (furylmethyl)phosphonium halide **3**.

(3-(Methoxycarbonyl)furan-2-ylmethyl)triphenylphosphonium Chloride (3a). Following procedure A, the starting materials 4-(triphenylphosphanylidene)acetic acid methyl ester (**1a**) (372 mg, 0.99 mmol) and chloracetaldehyde (**2a**) (85 mg, 1.1 mmol) yielded **3a** as a colorless solid (186 mg, 43%). ^1H NMR (250 MHz, $CDCl_3$): δ = 3.25 (s, 3H, OCH_3), 6.11 (d, $^2J_{H-P}$ = 15 Hz, 2H, PCH_2), 6.48 (d, ^3J = 2 Hz, 1H, H-4, Hetar) 7.25 (d ^3J = 2 Hz, 1H, H-5, Hetar), 7.45−7.60 (m, 6H, Ph), 7.65−7.85 (m, 9H, Ph). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 24.4, 51.6, 110.7, 117.4, 118.4, 130.0, 133.9, 135.0, 143.4, 148.5, 162.9. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3005 (w), 2850 (w), 1702 (s), 1602 (m), 1439 (s), 1321 (s), 1207 (m), 1112 (s), 766 (s), 741 (s), 691 (m), 527 (m), 500 (m). MS [EI, 70 eV; *m*/*z* (%)]: 400 ([M − HCl]$^+$, 100), 262 (46), 183 (44). MS [CI, NH_3; *m*/*z* (%)]: 401 ([M − Cl]$^+$, 5) 263 (100). Anal. Calcd for $C_{25}H_{22}ClO_3P$ (M_r = 436.87): C, 69.26; H, 5.36. Found: C, 69.00; H, 5.25.

General Procedure for the Synthesis of 2-Alkenylfurans 5. Procedure A. To a THF solution (5 mL; in the case solid aldehydes, 2.5 mL) of the phosphonium halide **3** was added *n*BuLi (1.0 equiv) at 0 °C. After the solution was stirring for 0.5 h at 0 °C, aldehyde **4** (1.0 equiv) was added; solid aldehydes were added as a THF solution or suspension (2.5 mL). The solution was stirred for 0.5 h at 0 °C and at 20 °C until the reaction was completed (4−25 h, TLC control). The mixture was poured into ice water (40 mL), and ether (100 mL) was added. The organic and the aqueous layer were separated, and the latter was extracted with ether (50 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, column i.d. = 2.0 cm). The starting materials were separated by elution with acetone, and the product was subsequently isolated by elution with methanol.

Procedure B. To a THF solution (10 mL) of the phosphonium halide **3** was added *n*BuLi (1.1 equiv) at 0 °C. After the solution was stirred for 0.5 h at 0 °C, aldehyde **4** (1.1−2.0 equiv) was added, and the solution was stirred for 72 h at 20 °C. The mixture was poured into ice water (40 mL), and ether (25 mL) was added. The organic and the aqueous layers were separated, and the latter was extracted with ether (5 × 25 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, 40:1 *n*-hexane/ethyl acetate; column, i.d. = 8.0 cm, height = 10 cm) and, subsequently, by HPLC (Lichrosorb 60, 7 μm, i.d. = 3.0 cm, l = 20 cm; eluent CH_2Cl_2).

Isopropyl 2-(Prop-1-enyl)furan-3-carboxylate (5a). The reaction of **3c** (503 mg, 1.12 mmol) with *n*BuLi (1.12 mmol) and acetaldehyde (**4a**) (49 mg, 1.12 mmol) was carried out as described in procedure A (reaction time 23 h). After purification by column chromatography (50:1 *n*-pentane/diethyl ether), **5a** was isolated as a yellow oil (130 mg, 62%, E/Z = 4:1); R_f = 0.35. ^{1}H NMR (250 MHz, $CDCl_3$, isomeric mixture): δ = 1.33 (d, ^3J = 6 Hz, 6H, 2 × CH_3), 1.92 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 3H, CH_3, *E*-isomer), 2.10 (dd, ^3J = 7 Hz, ^4J = 2 Hz, 3H, CH_3, *Z*-isomer), 5.17 (sept, ^3J = 6 Hz, 1H, OC*H*$(CH_3)_2$), 5.92 (dq, ^3J = 12 Hz, ^3J = 7 Hz, 1H, CH═CH, *Z*-isomer), 6.49 (dq, ^3J = 16 Hz, ^3J = 7 Hz, 1H, CH═CH, *E*-isomer), 6.65 (d, ^3J = 2 Hz, 1H, H-4, Hetar, *E*-isomer), 6.71 (d, ^3J = 2 Hz, 1H, H-4, Hetar, *Z*-isomer), 6.91 (dd, ^3J = 12 Hz, ^4J = 2 Hz, 1 H, CH═CH, *Z*-Isomer), 6.97 (dd, ^3J = 16 Hz, ^4J = 2 Hz, 1H, CH═CH, *E*-isomer), 7.21 (d, ^3J = 2 Hz, 1H, H-5, Hetar, *E*-isomer), 7.33 (d, ^3J = 2 Hz, 1H, H-5, Hetar, *Z*-isomer). ^{13}C (50.3 MHz, $CDCl_3$, *E*-isomer): δ = 18.6, 21.9, 67.6, 111.3, 112.5, 119.1 130.7, 140.4, 156.7, 163.2. IR (neat, cm^{-1}): $\tilde{\nu}$ = 2983 (m), 2936 (w), 1716 (s), 1453 (m), 1412 (m), 1378 (m), 1302 (m), 1183 (m), 1107 (s), 1025 (m), 840 (w), 756 (m), 605 (w). MS [EI, 70 eV; *m*/*z* (%)]: 194 (M^+, 35), 152 (100), 137 (60), 135 (42). Anal. Calcd for $C_{11}H_{14}O_3$ (M_r = 194.23): C, 68.02; H, 7.27. Found: C, 67.85; H, 6.94.

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Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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