mm); IR (film) 3340 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, 3 H, J = 6 Hz, CH_3CH), 1.4–2.3 (m, 4 H, CH_2CH_2), 3.45 (t, 2 H, J = 6 Hz, CH_2Br), 3.97 (m, 1 H, J = 6 Hz, HCOH) 7.80 (s, 1 H, HO).

Parallel reaction conditions employing tetrabutylammonium iodide (19.4 g, 52.5 mmol, Aldrich) as the halide source for 16 h afforded the 1-iodo-4-pentanol (**3**)[5] in 32% yield after chromatography (silica gel, eluted with ether). Standard treatment of this alcohol (16 h, 21 °C) with acetic anhydride (15 mL) and pyridine (3 mL) with a catalytic amount of 4-(dimethylamino)-pyridine (15 mg) afforded the acetate **4**: 3.26 g (80%); IR (film) 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, J = 6 Hz, CH_3CHOAc), 1.35–2.05 (m, 4 H, CH_2CH_2), 2.05 (s, 3 H, CH_3C=O), 3.21 (t, 2 H, J = 7 Hz, CH_2I), 4.85 (m, 1 H, HCOAc).

Reactioin of 2-methyltetrahydrofuran with anhydrous lithium bromide and boron trifluoride etherate in dichloromethane for 44 h gave **5** and **8** in approximately equal amounts on the basis of the integration of the methyl doublets at δ 1.29 and 1.40 in the ^1H NMR spectrum.

1-Acetoxy-4-bromopentane (9). Acetyl bromide (12.3 g, 100 mmol) in a pressure-equalizing dropping funnel was added dropwise over 20 min to a solution of 2-methyltetrahydrofuran (10.3 g, 120 mmol) containing zinc chloride (4 mg) maintained at 0 °C by an external ice bath. After addition was complete the ice bath was removed, the reaction stirred at 21 °C for 0.5 h and refluxed for 2.5 h. The reaction mixture was cooled, diluted with ether (130 mL), washed with 5% aqueous sodium bicarbonate solution, water, and brine, dried and the product purified by distillation to give **9**: 19.6 g (93%); bp 65–68 °C (2.5 mm) [lit.[12] bp 60 °C (0.01 mm)]; ^1H NMR ($CDCl_3$) δ 1.73 (d, 3 H, J = 6 Hz, CH_3CHBr), 1.7–1.9 (m, 4 H, CH_2CH_2), 2.00 (s, 3 H, CH_3OC=O), 4.01 (m, 3 H, CHBr, CH_2OAc). A weak doublet at δ 1.23 indicated the presence of ~10% of the positional isomer **6**.

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Alkylation of α-Formamido Ketone Enolate Anions. A Versatile Synthesis of α-Alkyl α-Amino Ketones[1]

Jack Ackrell and Joseph M. Muchowski*

Syntex Research, Institute of Organic Chemistry, Palo Alto, California 94304

Edvige Galeazzi and Angel Guzman

Syntex, S.A., División de Investigación, Lomas de Chapultepec, 11000 México, D.F.

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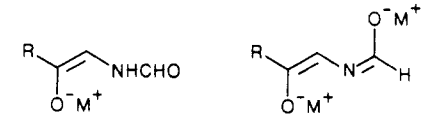
α-Amino ketones are essential components of the Knorr pyrrole synthesis[2] and also have considerable value as intermediates for the synthesis of adrenergic ethanolamine derivatives.[3] Numerous methods of preparing these compounds are known[4] and new processes to provide access thereto continue to be devised.[5] This paper describes a versatile synthesis of these compounds, which has been used routinely in these laboratories for several years, based on the α-alkylation of the enolate anions of α-formamido ketones.



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Garst et al.[6] have demonstrated that α-(*N*-alkyl-*N*-alkoxycarbonyl) ketones enolize predominantly toward the nitrogen atom[7] in the presence of various bases. This observation coupled with the facile hydrolysis of formamides under acidic conditions (e.g., see ref 8) suggested that α-formamido ketones might be useful building blocks for the construction of α-alkyl α-amino ketones. It was not obvious whether preferential carbon alkylation was more likely to take place on the mono (**1**) or dianionic (**2**) species, although it is clear that the inductive effect of the formamido group should enhance the acidity of the methylene hydrogens α thereto.[9] In any event, it was found that sequential reaction of α-formamidoacetophenone (**6**, R = Ph, Scheme I) with sodium hydride (1.07 equiv) and a primary alkyl halide (1.3 equiv) in dimethylformamide (DMF) at 0 °C gave the corresponding α-monoalkylated compounds **7** (R = Ph; R′ = Me, Et, *n*-Bu, $PhCH_2$) in 57–90% yields (Table I). Even 2-bromopropane gave the expected product in 30% yield, although in this case, an equivalent amount of the O-alkylated compound **9** (3:2 mixture of isomers) was also produced. The preferential mono-α-alkylation was not limited to formamidoacetophenone since the 3,4-methylenedioxy derivative (**6**, R = 3,4-$OCH_2OC_6H_3$) and 1-formamido-4-phenyl-2-butanone (**6**, R = $PhCH_2CH_2$) gave the anticipated compounds with methyl iodide, *n*-butyl bromide, and benzyl bromide. The latter substrate (**6**, R = $PhCH_2CH_2$) did, however, give rise to a greater proportion of other products (presumably because of competing alkylation at the α′-carbon atom and/or the nitrogen atom) and this is reflected in lower, but still useful, yields of the α-alkylated formamides.

The selective monoalkylation of α-formamido ketone enolates described herein is entirely analogous to that very recently reported by Hoye et al.[10] for benzamidoacetone (**10**, R = R′ = H) using strong bases such as lithium diisopropylamide (LDA), lithium bis(trimethylsilyl)amide, or potassium hydride in tetrahydrofuran solution (−78 to

Scheme I

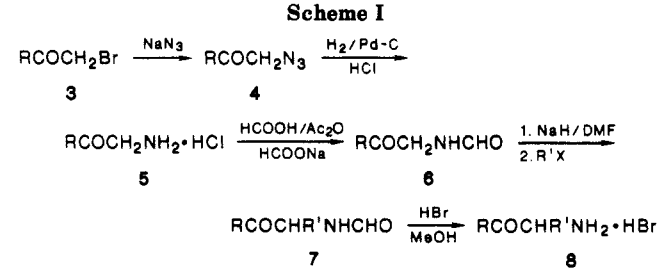

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Table I. Yields and Physical Constants of α-Alkyl α-Formamido Ketones 7

R	R^1	purifn method[a]	mp, °C (solvent)	yield, %	anal.[b]
Ph	Me	CC[c]	93–96 (acetone–hexane)	57	($C_{10}H_{11}NO_2$)
Ph	Et	cryst.	95–98 (ether)	67	($C_{11}H_{13}NO_2$)
Ph	*i*-Pr	TLC[d]	oil	30	($C_{12}H_{15}NO_2$)
Ph	*n*-Bu	CC[c]	oil	72	($C_{13}H_{17}NO_2$)
Ph	$PhCH_2$	CC[c]	oil	90	($C_{16}H_{15}NO_2$)
3,4-$OCH_2OC_6H_3$	Me	CC[e]	86–89 (acetone–hexane)	59	($C_{11}H_{11}NO_4$)
3,4-$OCH_2OC_6H_3$	*n*-Bu	CC[e]	oil	83	($C_{14}H_{17}NO_4$)
3,4-$OCH_2OC_6H_3$	$PhCH_2$	CC[e]	87–89 (acetone–hexane)	66	($C_{17}H_{15}NO_4$)
$PhCH_2CH_2$	Me	CC[f]	oil	28	($C_{12}H_{15}NO_2$)
$PhCH_2CH_2$	*n*-Bu	CC[f]	56–57 (acetone–hexane)	43	($C_{15}H_{21}NO_2$)
$PhCH_2CH_2$	$PhCH_2$	CC[f]	109–111 (acetone–hexane)	59	($C_{18}H_{19}NO_2$)

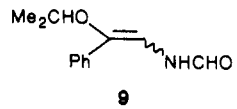
[a] CC = column chromatography on silica gel (100–150 g/g product); TLC = thin layer chromatography on silica gel. [b] The elemental analyses (C, H, N) of these compounds were within ±0.4% of the calculated values. [c] Gradient elution, hexane–EtOAC (90:10 to 70:30). [d] Hexane–EtOAC (3:1). [e] Gradient elution, hexane–EtOAC (80:20 to 40:60). [f] Gradient elution, hexane–EtOAC (90:10 to 50:50).

Table II. Yields and Physical Constants of the α-Azido Ketones 4, α-Amino Ketone Hydrochlorides 5, α-Formamido Ketones 6, and Related Compounds

compd	R	R^1	mp °C (solvent)	yield, %	anal.[a]	
4	Ph		oil[b]	95		
4	3,4-$OCH_2OC_6H_3$		93 (CH_2Cl_2–hexane)	85	($C_9H_7N_3O_3$)	C,H,N
4	$PhCH_2CH_2$		oil	95	($C_{10}H_{11}N_3O$)[c]	
5	Ph		195–197[d] (MeOH–acetone)	86	($C_8H_{10}ClNO$)	C,H,N,Cl
5	3,4-$OCH_2OC_6H_4$		213–215 (MeOH–acetone)	85	($C_9H_{10}ClNO_3$)	C,H, N, Cl
5	$PhCH_2CH_2$		136 (EtOAc)[e]	76		
6	Ph		80–82 (acetone–hexane)[f]	86		
6	3,4-$OCH_2OC_6H_4$		140–142 (acetone–hexane)	82	($C_{10}H_9NO_4$)	C,H,N
6	$PhCH_2CH_2$		oil	98	($C_{11}H_{13}NO_2$)	C,H,N
8	Ph	$PhCH_2$	249–250 (MeOH–ether)	94	($C_{15}H_{16}BrNO$)	C,H,N,Br
8	3,4-$OCH_2OC_6H_3$	$PhCH_2$	211–212 (MeOH–ether)	95	($C_{16}H_{16}BrNO_3$)	C,H,N,Br
8	$PhCH_2CH_2$	$PhCH_2$	197–199 (MeOH–ether)	77	($C_{17}H_{20}BrNO$)	C,H,N,Br
9			93–95 (EtOAc–ether)	30	($C_{15}H_{21}NO_2$)	C,H,N
11			151 (acetone–hexane)	19	($C_{23}H_{21}NO_2$)[g]	
12			oil	27	($C_{30}H_{27}NO_2$)[h]	

[a] The elemental analyses for these compounds were within ±0.4% of the calculated values. [b] Lit.[14] mp 17 °C. [c] Exact mass (high resolution mass spectrum) calcd for $C_{10}H_{11}N_3O$ 189.0902, found 189.0904. [d] Lit.[15] mp 188 °C. [e] Lit.[16] mp 139–140 °C. [f] Lit.[17] mp 81–82 °C. [g] Exact mass (high resolution mass spectrum) calcd for $C_{23}H_{21}NO_2$ 343.1572, found 343.1566. [h] Exact mass (high resolution mass spectrum) calcd for $C_{30}H_{27}NO_2$ 433.2042, found 433.2036.

0 °C). In addition, these authors reported that the monoalkylated compound could be α,α-dialkylated. Indeed, geminal dialkylation seems to have been a troublesome competing reaction when mono-α-alkylation was attempted with alkyl halides less reactive than methyl iodide (e.g., $PhCH_2Br$, *n*-BuI). In contrast, under the conditions described in this paper, geminally dialkylated products were formed only in very small amounts. A deliberate attempt to prepare such a compound from formamidoacetophenone **6** (R = Ph) and 2 equiv of benzyl bromide in the presence of 2 equiv of sodium hydride gave mixtures of the previously described mono-α-benzyl derivative **7** (R = Ph, R′ = $PhCH_2$), the α,α-dibenzyl compound **11** and the trialkylated formamide **12** in an approximately 1:2:3 ratio. It would thus appear that although monoalkylation of **6** (R = Ph) does occur rapidly, α,α-dialkylation can indeed take place if the conditions are appropriately modified.



9

$CH_3COCRR'NHCOPh$

10

$PhCOC(CH_2Ph)_2NHCHO$

11

$PhCOC(CH_2Ph)_2N(CH_2Ph)CHO$

12

The formamides **7** were rapidly (1 h) cleaved with methanolic hydrogen bromide (10 equiv) at reflux temperature. Thus, the α-benzyl compounds **8** (R = Ph, 3,4-$OCH_2OC_6H_3$, $PhCH_2CH_2$; R′ = $PhCH_2$) were isolated as the crystalline hydrobromide salts in 94%, 95%, and 77% yields, respectively. Inasmuch as the α-formamido ketones **6** are easily prepared in three steps from the bromo ketones **3** (see Scheme I and the Experimental Section), the process described herein constitutes a most useful, indeed, the preferred, synthesis of α-alkyl α-amino ketones.

Experimental Section

The melting points were determined in a Mel Temp apparatus and are not corrected. The IR spectra were measured on a Sargent-Welch Model 3-200 IR spectrophotometer or a Perkin-Elmer Model 237 grating IR spectrophotometer. The NMR spectra were measured with a Varian EM-390 or a Bruker WM300 spectrometer. The high resolution mass spectra were obtained with a Finnigan MAT 311A mass spectrometer. The low resolution mass spectrum was measured with a Finnigan MAT 112S mass spectrometer. Phenacyl bromide was purchased from a commercial source; 3,4-(methylenedioxy)phenacyl bromide[11] and 1-bromo-4-phenyl-2-butanone[12] were literature compounds.

Preparation of the α-Azido Ketones 4. Solid sodium azide (4.0 g, 61 mmol) was added to a solution (or suspension) of the bromo ketone (50 mmol) in dimethyl sulfoxide (30 mL) with stirring in one portion at 10 °C. After stirring for 0.5 h at this temperature, the mixture was poured into water and the product was extracted into ethyl acetate. The extract was washed with water, dried over sodium sulfate, and then evaporated in vacuo. The residual azide was usually sufficiently pure to be used in the next step. The yields and physical constants of these compounds are found in Table II.

After crystallization from dichloromethane–hexane, 3,4-(methylenedioxy)phenacyl azide (**4**, R = 3,4-$OCH_2OC_6H_3$) had the following: mp 93 °C; UV (MeOH) 229 nm, 273, 309 (ε 17 400, 6760,

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8130); IR ($CHCl_3$) 2114, 1695 cm^{-1}, NMR ($CDCl_3$) δ 4.45 (s, 2 H, CH_2N), 6.06 (s, 2 H, OCH_2O), 6.80 (m, 2 H, aryl H's), 6.85 (d, 1 H, J_{ortho} = 7.5 Hz, H-5).

Preparation of the α-Amino Ketone Hydrochlorides 5. A solution of the azido ketone (400 mmol) in methanol (300 mL) containing hydrogen chloride (400 mmol) and suspended 10% palladium on charcoal catalyst (4 g) was hydrogenated at 45 psig at room temperature for 5 h. The mixture was filtered, the filtrate was evaporated in vacuo, and the residue was crystallized from a suitable solvent system. The yields and physical constants of these compounds are found in Table II.

1-Amino-4-phenyl-2-butanone hydrochloride (*5*, R = $PhCH_2CH_2$) was typical of this group of compounds: mp 136 °C (EtOAc); UV (MeOH) 242 nm, 247, 251, 260, 262, 266 (ϵ 1413, 676, 190, 224, 209, 190, 170); IR (KBr) 3448, 1718 cm^{-1}; NMR (Me_2SO-d_6) δ 2.86 (s, 4 H, CH_2CH_2) 3.91 (s, 2 H, CH_2), 7.26 (s, 5 H, aryl H's), 8.43 [s, 3 H, NH_3 (broad, exchanged with D_2O)].

Synthesis of the α-Formamido Ketones 6. Anhydrous sodium formate (15 g, 220 mmol) was suspended in acetic–formic anhydride (90 mL, prepared from acetic anhydride (60 mL) and 97% formic acid (30 mL) according to the procedure of Olah[13]) and stirred at room temperature for 10 min. The amino ketone hydrochloride (165 mmol) was added all at once and stirring at room temperature was continued for 1 h. The reaction mixture was poured into cold water (500 mL) and the product was extracted into dichloromethane. The extract was washed with water and then shaken with solid sodium carbonate (50 g, 470 mmol). The mixture was filtered and the filtrate was evaporated in vacuo to give the crude formamide. See Table II for yields and physical constants.

3,4-(Methylenedioxy)phenacylformamide (**6**, R = 3,4-$OCH_2OC_6H_3$) was typical of this class of compounds: mp 140–142 °C (acetone–hexane): UV (MeOH) 229 nm, 272, 307 (ϵ 18600, 7080, 8130); IR ($CHCl_3$) 3413, 1695, 1675 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 4.68 (d, 2 H, J = 3 Hz, CH_2N), 6.06 (s, 2 H, OCH_2O), 6.86 (d, 1 H, J = 9 Hz, H-6), 7.50 (m, 3 H, H-3, H-5, NH), 8.31 (s, 1 H, CHO).

Preparation of the α-Alkyl α-Formamido Ketones 7. The α-formamido ketone **6** (6 mmol) in anhydrous DMF (10 mL) was added to a stirred and cooled (0 °C) suspension of sodium hydride (60% in mineral oil; 0.257 g, 6.4 mmol) in dry DMF (20 mL) maintained in a nitrogen atmosphere. After 30 min the alkyl halide (8 mmol) was added slowly at 0 °C and 1 h thereafter the reaction mixture was poured into cold water. The product was extracted into ethyl acetate, and the extract was washed well with water, dried (Na_2SO_4), and evaporated in vacuo. The crude α-alkylated compounds were purified by the methods described in Table I.

Alkylation of **6** (R = Ph) with 2-bromopropane gave a 1:1 mixture of **7** (R = Ph; R′ = *i*-Pr) and the enol ether **9** (3:2 mixture of isomers) which was separated by TLC (see Table I). The enol ether mixture was a solid: UV (MeOH) 222 nm, 283 (ϵ 9550, 20400); NMR ($CDCl_3$) δ 1.24 (d, 6 H, J = 6 Hz, *i*-Pr), 4.11 (septet, 1 H, J = 6 Hz, CH), 6.90, 7.01 (singlets, total 1 H, CH), 7.34 (m, 5 H, aryl H's), 7.56 (broad, 1 H, NH), 8.22 (s, 1 H, CHO). The spectral characteristics of the desired α-alkylated compound **7** (R = Ph; R′ = *i*-Pr), an oil, were quite different: UV (MeOH) 245 nm (ϵ 12300); NMR ($CDCl_3$) δ 0.77 (d, 3 H, J = 6.7 Hz, Me_2CH), 1.04 (d, 3 H, J = 6.7 Hz, Me_2CH), 2.20 (m, 1 H, $CHMe_2$), 5.68 (dd, 1 H, J = 3.9, 10.1 Hz, CH), 6.50 (broad, 1 H, NH), 7.53 (m, 3 H, H-3,4,5), 8.02 (m, 2 H, H-2,6), 8.36 (s, 1 H, CHO).

Attempted Dialkylation of Formamidoacetophenone (6, R = Ph). Formamidoacetophenone (1.00 g, 6.1 mmol) was reacted with a suspension of 60% sodium hydride (0.539 g, 13.5 mmol) in anhydrous DMF (10 mL) and benzyl bromide (2.3 g, 13 mmol) at 0 °C as described above. After 1 h the reaction mixture was worked up in the usual way and the crude product was subjected to preparative thin layer chromatography on silica gel using hexane–ethyl acetate (70:30) as the developing solvent. There was thus obtained the mono- (0.15 g, 10%), di- (0.400 g, 19%), and tribenzyl (0.720 g, 27%) compounds **7** (R = Ph; R′ = $PhCH_2$), **11** and **12**, respectively. The monobenzyl compound was an oil: UV (MeOH) 245 nm, 280 (ϵ 12900, 1320); IR ($CHCl_3$) 3413, 1695, 1669 cm^{-1}; NMR ($CDCl_3$) δ 3.15 (m, 2 H, CH_2), 5.88 (m, 1 H, CH), 6.66 (broad, 1 H, NH), 7.06–7.50 (m, 8 H, aryl H's), 7.96 (m, 2 H, aryl H's), 8.20 (s, 1 H, CHO). The dibenzyl compound **11** was a solid which after crystallization from acetone–hexane had the following: mp 151 °C; UV (MeOH) 219 nm, 250 (ϵ 10200, 10100); IR ($CHCl_3$) 3367, 1668, 1689 cm^{-1}; NMR ($CDCl_3$) δ 3.75 (d, 2 H, J = 13.5 Hz, CH_2), 4.20 (d, 2 H, J = 13.5 Hz, CH_2), 6.63 (s, 1 H, NH), 7.50 (m, 13 H, aryl H's), 7.86 (m, 2 H, aryl H's), 8.16 (s, 1 H, CHO). The tribenzyl compound **12** also was an oil; UV (MeOH) 223 nm 2.45 (ϵ 11200, 9330); IR ($CHCl_3$) 1661 cm^{-1}; NMR ($CDCl_3$) δ 3.30 (q, 2 H, J = 13.5 Hz, CH_2), 3.50 (q, 2 H, J = 13.4 Hz, CH_2), 3.79, 4.75 (broad singlets, total 2 H, NCH_2), 7.03 (m, 2 H), 7.15–7.50 (m, 16 H), 7.58 (dd, 1 H), 7.84 (dd, 1 H), 7.89, 8.13 (singlets, total 1 H, CHO); mass spectrum, *m/e* (relative intensity) 342 (14, $M^+ - C_7H_7$), 328 (14, $M^+ - C_6H_5CO$), 314 (20, $M^+ - C_7H_7 - CO$), 300 (7, $M^+ - C_7H_7NCHO + H^+$), 91 (100, C_7H_7).

Synthesis of the α-Alkyl α-Amino Ketone Hydrobromides 8. Methanolic hydrogen bromide (16.7 mL of a 3 N solution, 50 mmol) was added to a solution of **7** (5 mmol) in methanol (50 mL) and the solution was heated at reflux temperature for 1 h. The solvent was removed in vacuo and the residue was crystallized from a methanol–ether solution. See Table II for yields and physical constants.

1,5-Diphenyl-2-amino-3-pentanone hydrobromide (**8**, R = $PhCH_2CH_2$; R′ = $PhCH_2$): mp 197–199 °C; UV (MeOH) 220 nm, 248, 253, 258, 264, 267 (ϵ 3720, 229, 309, 398, 331, 251); IR (KBr) 3175, 1718 cm^{-1}; NMR (Me_2SO-d_6) δ 2.73 (s, 4 H, CH_2CH_2), 3.05 (d, J = 6 Hz, CH_2), 4.40 (t, 1 H, CH), 7.16 (m, 10 H, aromatic H's), 8.25 (broad, 3 H, NH_3, enchanged with D_2O).

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Registry No. **3** (R = Ph), 70-11-1; **3** (R = 3,4-$OCH_2OC_6H_3$), 40288-65-1; **3** (R = $PhCH_2CH_2$), 31984-10-8; **4** (R = Ph), 1816-88-2; **4** (R = 3,4-$OCH_2OC_6H_3$), 102831-07-2; **4** (R = $PhCH_2CH_2$), 102831-08-3; **5** (R = Ph), 5468-37-1; **5** (R = 3,4-$OCH_2OC_6H_3$), 38061-34-6; **5** (R = $PhCH_2CH_2$), 31419-53-1; **6** (R = Ph), 73286-37-0; **6** (R = 3,4-$OCH_2OC_6H_3$), 102831-09-4; **6** (R = $PhCH_2CH_2$), 102831-10-7; **7** (R = Ph, R^1 = Me), 102831-14-1; **7** (R = Ph, R^1 = Et), 102831-15-2; **7** (R = Ph, R^1 = Pr-*c*), 102831-16-3; **7** (R = Ph, R^1 = Bu), 102831-17-4; **7** (R = Ph, R^1 = CH_2Ph), 102831-18-5; **7** (R = 3,4-$OCH_2OC_6H_3$, R^1 = Me), 102831-19-6; **7** (R = 3,4-$OCH_2OC_6H_3$, R^1 = Bu), 102831-20-9; **7** (R = 3,4-$OCH_2OC_6H_3$, R^1 = CH_2Ph), 102831-21-0; **7** (R = CH_2CH_2Ph, R^1 = Me), 102831-22-1; **7** (R = CH_2CH_2Ph, R^1 = Bu), 102831-23-2; **7** (R = CH_2CH_2Ph, R^1 = CH_2Ph), 102831-24-3; **8** (R = Ph, R^1 = CH_2Ph), 102831-11-8; **8** (R = 3,4-$OCH_2OC_6H_3$, R^1 = CH_2Ph), 102831-12-9; **8** (R = CH_2CH_2Ph, R^1 = CH_2Ph), 102831-13-0; (*E*)-**9**, 102831-25-4; (*Z*)-**9**, 102831-28-7; **11**, 102831-26-5; **12**, 102831-27-6; MeI, 74-88-4; EtBr, 74-96-4; *i*-PrBr, 75-26-3; BuBr, 109-65-9; $PhCH_2Br$, 100-39-0.

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Improved Route to 3-Vinyl-Substituted Cyclopentanones. Synthesis of (±)-Mitsugashiwalactone†

William A. Nugent* and Frank W. Hobbs, Jr.

Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

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Recently we described[1] a simple route to 2,3-disubstituted cyclopentanones. The procedure utilizes an efficient catalytic dimerization[2,3] of methyl acrylate (eq 1) to afford

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