Application of the Acetate of Baylis-Hillman Adducts of Salicylaldehydes in the Synthesis of Methyl 2-Oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates

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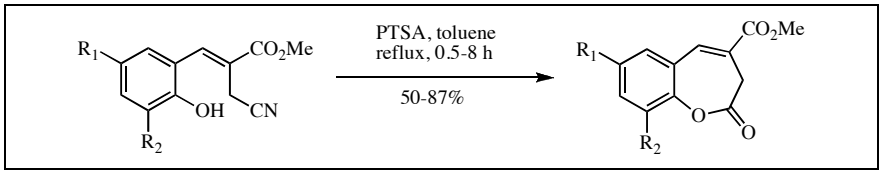

A simple synthesis of several methyl 2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates from Baylis-Hillman adducts of *O*-benzyl protected 2-hydroxybenzadehydes has been described through the acetylation, cyanation, debenzylation, as well as acid assisted Pinner cyclization.

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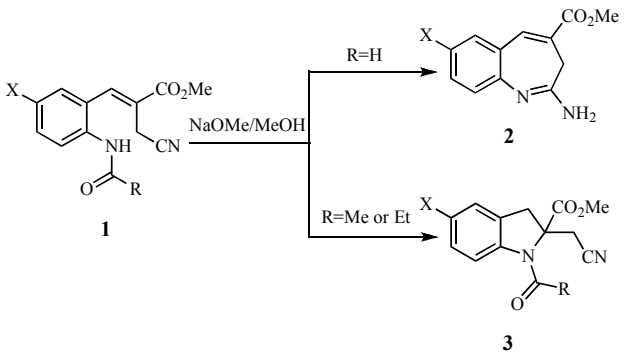
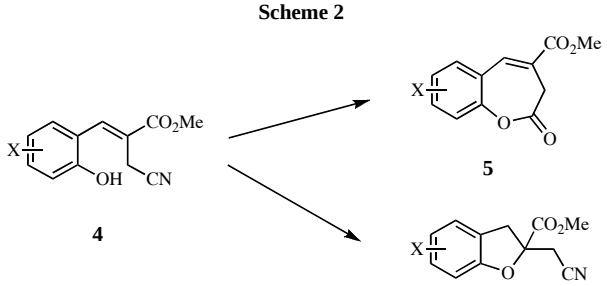
The Baylis-Hillman (BH) reaction [1] has attracted the attention of organic chemists in recent years as this reaction provides synthetically useful multifunctional molecules that have been successfully employed in the synthesis of various heterocycles. During continued efforts to develop Baylis-Hillman chemistry [2], we recently reported [3] that methyl 2-amino-3*H*-1-benzazepine-4-carboxylates **2** or methyl 2-(cyanomethyl)-2,3-dihydro-1*H*-indole-2-carboxylates **3** were prepared from the reaction of methyl 2-(cyanomethyl)-3-(2-acylaminophenyl)propenoates **1**, which were readily obtained from BH adducts of *N*-protected 2-aminobenzaldehydes, with sodium methoxide in methanol as shown in Scheme 1. We envisioned that we could synthesize methyl 2-oxo-2,3-dihydrobenzo[*b*]-oxepine-4-carboxylates **5** or 2,3-dihydrobenzofurans **6** by the cyclization of methyl 2-(cyanomethyl)-3-(2-hydroxyphenyl)propenoates **4** (Scheme 2).

The Baylis-Hillman reactions of salicylaldehydes with acrylic acid esters are well known [4] to afford a mixture of coumarins and chromenes, directly. So, treatment of several known *O*-benzyl protected 2-hydroxybenzaldehydes **8a**-**f** with 3 equivalents of methyl acrylate and triethanolamine in the presence of 1 equivalent of 1,4-diazabicyclo[2,2,0]octane (DABCO) without solvent at room temperature produced BH adducts, methyl 3-(2-benzyloxy)phenyl-3-hydroxy-2-methylenepropanoates **9a**-**f** in 69-95% yields. The reaction of **9a**-**f** with acetic anhydride in the presence of a catalytic amount of 4-(dimethylamino)pyridine(DMAP) in dichloromethane at room temperature gave BH acetates **10a**-**f** in 85-98% yields. The cyanation reaction of the acetates **10a**-**f** with potassium cyanide [3,5] in dimethyl sulfoxide-water (3:1) at room temperature occurred in an S_N2' fashion to give

Scheme 1

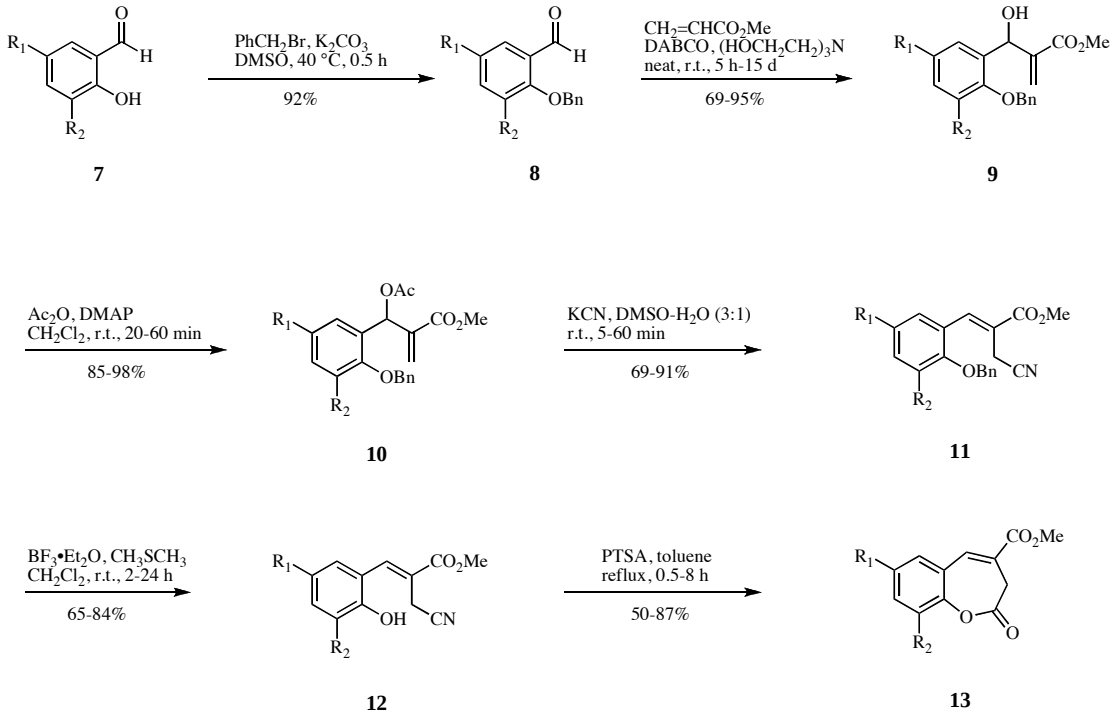


Scheme 2



methyl 3-(2-benzyloxy)phenyl-2-(cyanomethyl)propenoates **11a**-**f** (69-91%). In all cases, the stereoselectivity was found to be 100% *E*-selectivity, as determined by ^{1}H nmr analysis of alkene and methylene protons by comparison with literature values [3]. Debenzylation of **11a**-**f** using boron trifluoride etherate and dimethyl sulfide [6] in dichloromethane gave the required key intermediate methyl 3-(2-hydroxyphenyl)-2-(cyanomethyl)propenoates **12a**-**f** in 65-84% yields. We investigated the intramolecular Pinner cyclization reaction [7] using **12a**-**f** with *para*-toluene-

Scheme 3



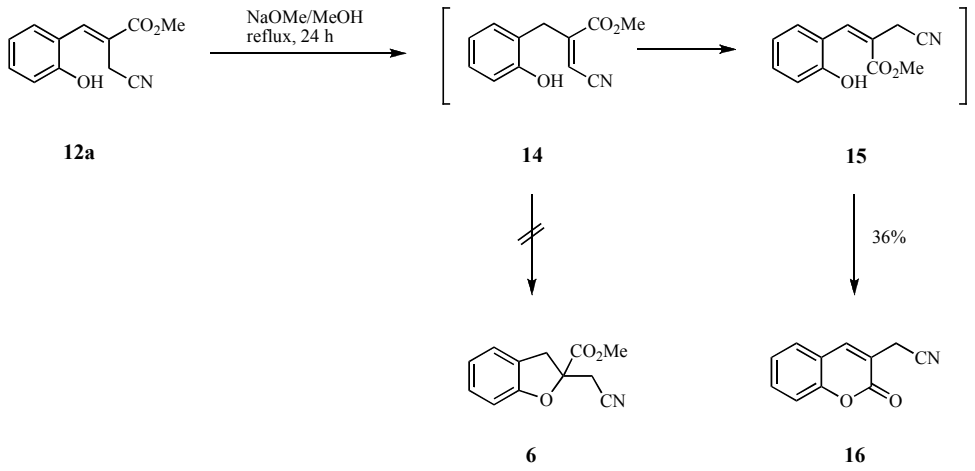
7 **8** **9** **10** **11** **12** **13**

7-13	a	b	c	d	e	f
R_1	H	Br	H	Me	NO_2	Cl
R_2	H	H	OEt	H	H	Cl

sulfonic acid in toluene. After stirring the mixture at reflux temperature for 0.5-8 hours, the desired methyl 2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates **13a**-**f** were obtained in 50-87% yields. Electron-donating or electron-withdrawing substituted compounds gave the corresponding benzoxepines in reasonable yields (Scheme 3).

Next we examined a reaction using **12a** with sodium methoxide in methanol. After stirring the mixture at reflux temperature for 24 hours, the only product 3-cyanomethyl coumarin **16** was obtained in a disappointing yield (36%) along with the recovered starting compound **12a** (25%). When using excess base the increase of yield was

Scheme 4



12a **14** **15** **6** **16**

unsuccessful. Apparently under these reaction conditions, base-promoted *E*/*Z* isomerization took place preferentially to give **15**, followed by subsequent formation of lactone to produce coumarin **16**. The possible dihydrobenzofuran **6** was not obtained (Scheme 4).

The selective synthesis of seven-membered ring lactones, fused to an aromatic ring, is of considerable interest due to their presence in biologically and pharmacologically active compounds [8]. Several approaches to such benzoxepines involve cyclization of (*E*)-itaconic half-esters with sodium acetate in boiling acetic anhydride [9], intramolecular cyclocarbonylation of 2-allylphenols catalyzed by palladium complex [10], allenyl alcohols catalyzed by a ruthenium complex [11], cyclization of 2-iodobenzyl alcohols with propiolates catalyzed by $Ni(dppe)Br_2$ and zinc powder [12], the rhodium-catalyzed carbon-carbon bond cleavage of cyclobutanone [13], and the ring closing methathesis reaction of acrylic ester of 2-allylphenol [14].

In summary, a new method for the synthesis of methyl 2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates from Baylis-Hillman adducts of *O*-benzyl protected 2-hydroxybenzaldehydes has been developed through the acetylation, cyanation, debenzylation, as well as acid assisted cyclization.

EXPERIMENTAL

Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC plates. Melting points were measured by an Electrothermal melting point apparatus and were uncorrected. Microanalysis was obtained using a Thermo Electron Corporation Flash EA 1112 element analyzer. Infrared spectra were recorded with a Nicolet Magna 550 FTIR spectrometer. The ^1H and ^{13}C nmr spectra were measured on a Gemini 300 spectrometer using deuteriochloroform. All chemical shifts are reported in parts per million relative to tetramethylsilane. The coupling constants (J) are expressed in Hertz.

The known 2-benzyloxybenzaldehydes **8a** [15], **8b** [16], **8c** [17], **8d**, **8e** [18] and BH adducts **9a** [19], **9b**, **9c** [20] were prepared according to literature procedure.

2-(Benzyloxy)-3,5-dichlorobenzaldehyde (8f) [21]. A mixture of **7f** (3.82 g, 10 mmoles), benzyl bromide (1.31 ml, 11 mmoles), and potassium carbonate (1.52 g, 11 mmoles) in dimethyl sulfoxide (10 ml) was stirred at 40 ℃ for 30 minutes. The mixture was diluted with water (20 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **8f** (2.59 g, 92%) as a white solid; mp: 81-83℃; ir (potassium bromide): 1693 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.14 (s, 2 H), 7.35-7.41 (m, 5 H), 7.67 (m, 2 H), 9.98 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 77.7, 126.5, 128.9, 129.0, 129.2, 130.0, 130.6, 132.0, 134.8, 135.7, 155.9, 187.6. *Anal*. Calcd. for $C_{14}H_{10}Cl_2O_2$: C, 59.81; H, 3.59. Found: C, 59.68; H, 3.82.

Methyl 3-(2-Benzyloxy-5-methyl)phenyl-3-hydroxy-2-methylenepropanoate (9d). A mixture of **8d** (2.26 g, 10 mmoles), methyl acrylate (2.7 ml, 30 mmoles), DABCO (1.12 g, 10 mmoles), and triethanolamine (1.07 ml, 8 mmoles) was stirred at room temperature for 15 days. The mixture was diluted with water (20 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **9d** (2.14 g, 69%) as a white solid; mp 58.5 - 59.5 ℃; ir (potassium bromide): 3417, 1721 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (s, 3 H), 3.38 (d, 1 H, J = 6.3 Hz), 3.73 (s, 3 H), 5.06 (s, 2 H), 5.69 (s, 1 H), 5.91 (d, 1 H, J = 6.3 Hz), 6.29 (s, 1 H), 6.81-6.83 (m, 1 H), 7.02-7.05 (m, 1 H), 7.18-7.19 (m, 1 H), 7.31-7.45 (m, 5 H); ^{13}C nmr (deuteriochloroform): δ 20.6, 51.9, 68.4, 70.3, 111.9, 125.9, 127.3, 127.9, 128.3, 128.5, 129.1, 130.3, 136.9, 141.3, 153.6, 167.1. *Anal*. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.33; H, 6.24.

Methyl 3-(2-Benzyloxy-5-nitro)phenyl-3-hydroxy-2-methylenepropanoate (9e). A mixture of **8e** (1.29 g, 5 mmoles), methyl acrylate (1.35 ml, 15 mmoles), DABCO (0.56 g, 5 mmoles), and triethanolamine (0.53 ml, 4 mmoles) was stirred at room temperature for 4 hours. The mixture was diluted with water (10 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **9e** (1.63 g, 95%) as a white solid; mp 87.5-89 ℃; ir (potassium bromide): 3477, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.41 (d, 1 H, J = 6.1 Hz), 3.74 (s, 3 H), 5.18 (s, 2 H), 5.66 (s, 1 H), 5.93 (d, 1 H, J = 6.1 Hz), 6.32 (s, 1 H), 6.99 (d, 1 H, J = 9.2 Hz), 7.33-7.43 (m, 5 H), 8.17 (dd, 1 H, J = 9.2 and 2.8 Hz), 8.39 (d, 1 H, J = 2.8 Hz); ^{13}C nmr (deuteriochloroform): δ 52.1, 67.5, 71.0, 111.4, 123.7, 125.1, 127.0, 127.4, 128.6, 128.8, 131.0, 135.2, 140.1, 141.7, 160.2, 166.7. *Anal*. Calcd. for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 62.78; H, 4.76; N, 3.89.

Methyl 3-(2-Benzyloxy-3,5-dichloro)phenyl-3-hydroxy-2-methylenepropanoate (9f). A mixture of **8f** (1.41 g, 5 mmoles), methyl acrylate (1.35 ml, 15 mmoles), DABCO (0.56 g, 5 mmoles), and triethanolamine (0.53 ml, 4 mmoles) was stirred at room temperature for 6 hours. The mixture was diluted with water (10 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **9f** (1.74 g, 95%) as an oil; ir (potassium bromide): 3431, 1716 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.79 (d, 1 H, J = 5.1 Hz), 3.72 (s, 3 H), 5.08 (two d, 2 H, J = 11.0 Hz), 5.76 (s, 1 H), 5.80 (d, 1 H, J = 5.1 Hz), 6.35 (s, 1 H), 7.27-7.48 (m, 7 H); ^{13}C nmr (deuteriochloroform): δ 52.1, 67.2, 75.4, 126.6, 126.8, 128.4, 128.5, 128.6, 128.8, 129.9, 136.3, 138.1, 140.5, 151.0, 160.7, 166.4. *Anal*. Calcd. for $C_{18}H_{16}Cl_2O_4$: C, 58.87; H, 4.39. Found: C, 58.65; H, 4.41.

Preparation of BH Acetates 10: General Procedure. Acetic anhydride (1.42 ml, 15 mmoles) and 4-(dimethylamino)pyridine (0.22 g, 2 mmoles) were added to a stirred solution of BH adduct **9** (10 mmoles) in dichloromethane (15 ml) at room temperature. After stirring for 20-60 minutes the reaction mixture was diluted with saturated aqueous sodium bicarbonate

solution (10 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **10** as an oil or solid.

The physical and spectral data of **10** prepared by this general method follows.

Methyl 3-Acetoxy-3-(2-benzyloxy)phenyl-2-methylenepropanoate (10a). Reaction time: 20 minutes; oil; yield: 95%; ir (neat): 1744, 1726 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.08 (s, 3 H), 3.69 (s, 3 H), 5.11 (s, 2 H), 5.65 (s, 1 H), 6.40 (s, 1 H), 6.91-6.97 (m, 2 H), 7.14 (s, 1 H), 7.23-7.42 (m, 7 H); ^{13}C nmr (deuteriochloroform): δ 21.0, 51.9, 68.2, 70.0, 112.2, 120.7, 126.4, 127.0, 127.3, 127.7, 128.4, 129.5, 136.9, 139.0, 155.8, 165.7, 169.4. *Anal*. Calcd. for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.39; H, 5.74.

Methyl 3-Acetoxy-3-(2-benzyloxy-5-bromo)phenyl-2-methylenepropanoate (10b). Reaction time: 30 minutes; oil; yield: 98%; ir (neat): 1747, 1728 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.10 (s, 3 H), 3.70 (s, 3 H), 5.10 (s, 2 H), 5.67 (s, 1 H), 6.42 (s, 1 H), 6.78-6.80 (m, 1 H), 7.07 (s, 1 H), 7.29-7.39 (m, 7 H); ^{13}C nmr (deuteriochloroform): δ 21.0, 52.0, 67.5, 70.3, 113.0, 114.0, 127.0, 127.8, 127.9, 128.5, 128.8, 130.5, 132.1, 136.3, 138.5, 154.8, 165.4, 169.3. *Anal*. Calcd. for $C_{20}H_{19}BrO_5$: C, 57.29; H, 4.57. Found: C, 57.05; H, 4.39.

Methyl 3-Acetoxy-3-(2-benzyloxy-3-ethoxy)phenyl-2-methylenepropanoate (10c). Reaction time: 30 minutes; white solid; yield: 85%; mp: 63-64.5 ℃; ir (potassium bromide): 1745, 1727 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.46 (t, 3 H, J = 7.0 Hz), 2.06 (s, 3 H), 3.68 (s, 3 H), 4.09 (q, 2 H, J = 7.0 Hz), 5.11 (s, 2 H), 5.59 (s, 1 H), 6.37 (s, 1 H), 6.87-7.07 (m, 3 H), 7.12 (s, 1 H), 7.28-7.54 (m, 5 H); ^{13}C nmr (deuteriochloroform): δ 14.9, 21.0, 51.9, 64.2, 68.3, 74.6, 113.5, 119.4, 124.0, 127.4, 127.8, 128.2, 128.3, 131.7, 137.7, 139.0, 145.9, 152.1, 165.6, 169.4. *Anal*. Calcd. for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.61; H, 6.06.

Methyl 3-Acetoxy-3-(2-benzyloxy-5-methyl)phenyl-2-methylenepropanoate (10d) Reaction time: 1 hour; oil; yield: 98%; ir (dichloromethane): 1745, 1726 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.09 (s, 3 H), 2.27 (s, 3 H), 3.69 (s, 3 H), 5.09 (s, 2 H), 5.67 (s, 1 H), 6.41 (s, 1 H), 6.80-6.83 (m, 1 H), 7.04-7.07 (m, 2 H), 7.13 (s, 1 H), 7.28-7.41 (m, 5 H); ^{13}C nmr (deuteriochloroform): δ 20.6, 21.0, 51.9, 68.2, 70.1, 112.3, 126.1, 127.0, 127.1, 127.7, 128.3, 128.4, 129.9, 130.0, 137.1, 139.1, 153.8, 165.7, 169.5. *Anal*. Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.32; H, 6.31.

Methyl 3-Acetoxy-3-(2-benzyloxy-5-nitro)phenyl-2-methylenepropanoate (10e). Reaction time: 30 minutes; white solid; yield: 91%; mp: 80-82.5 ℃; ir (potassium bromide): 1747, 1727 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.13 (s, 3 H), 3.70 (s, 3 H), 5.23 (s, 2 H), 5.73 (s, 1 H), 6.47 (s, 1 H), 6.98-7.01 (m, 1 H), 7.08 (s, 1 H), 7.32-7.40 (m, 5 H), 8.17-8.22 (m, 2 H); ^{13}C nmr (deuteriochloroform): δ 20.9, 52.1, 67.3, 70.9, 111.8, 123.8, 125.7, 127.1, 128.0, 128.3, 128.4, 128.7, 135.2, 137.9, 141.4, 160.5, 165.2, 169.3. *Anal*. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.11; H, 4.88; N, 3.42.

Methyl 3-Acetoxy-3-(2-benzyloxy-3,5-dichloro)phenyl-2-methylenepropanoate (10f). Reaction time: 30 minutes; oil; yield: 90%; ir (potassium bromide): 1748, 1728 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.10 (s, 3 H), 3.70 (s, 3 H), 5.11 (two d, 2 H, J = 13.4 Hz), 5.64 (s, 1 H), 6.42 (s, 1 H), 7.04 (s, 1 H), 7.20-7.21 (m, 1 H), 7.32-7.42 (m, 4 H), 7.52-7.55 (m, 2 H); ^{13}C nmr (deuteriochloroform): δ 20.9, 52.1, 67.7, 75.4, 126.8, 128.0, 128.3, 128.4, 128.5, 129.3, 129.7, 130.5, 134.7, 136.3, 138.2, 151.5, 165.1, 169.2. *Anal*. Calcd. for $C_{20}H_{18}Cl_2O_5$: C, 58.69; H, 4.43. Found: C, 58.72; H, 4.56.

Preparation of Methyl 3-(2-Benzyloxy)phenyl-2-(cyanomethyl)propenoates 11: General Procedure. Potassium cyanide (0.49 g, 7.5 mmoles) was added to a stirred solution of BH acetate **10** in aqueous dimethyl sulfoxide (1:3, 10 ml) at room temperature. After stirring for 5-60 minutes the reaction mixture was diluted with water (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **11** as an oil or solid.

The physical and spectral data of **11** prepared by this general method follows.

Methyl (*E*)-3-(2-Benzyloxy)phenyl-2-(cyanomethyl)propenoate (11a). Reaction time: 1 hour; oil; yield: 77%; ir (neat): 2250, 1713 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.46 (s, 2 H), 3.88 (s, 3 H), 5.16 (s, 2 H), 6.97-7.07 (m, 2 H), 7.31-7.39 (m, 7 H), 8.12 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.4, 52.6, 70.4, 112.8, 117.6, 121.1, 122.0, 123.3, 127.1, 128.1, 128.6, 129.8, 131.3, 136.4, 140.5, 156.6, 166.2. *Anal*. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.04; H, 5.38; N, 4.34.

Methyl (*E*)-3-(2-Benzyloxy-5-bromo)phenyl-2-(cyanomethyl)propenoate (11b). Reaction time: 20 minutes; pale yellow solid; yield: 85%; mp: 94-95℃; ir (potassium bromide): 2252, 1714 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.43 (s, 2 H), 3.89 (s, 3 H), 5.14 (s, 2 H), 6.85-6.88 (m, 1 H), 7.30-7.45 (m, 7 H), 7.97 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.3, 52.8, 70.7, 113.2, 114.6, 117.1, 123.4, 125.2, 127.1, 128.2, 128.7, 132.1, 133.7, 135.8, 138.9, 155.5, 165.8. *Anal*. Calcd. for $C_{19}H_{16}BrNO_3$: C, 59.08; H, 4.18; N, 3.63. Found: C, 59.24; H, 3.91; N, 3.40.

Methyl (*E*)-3-(2-Benzyloxy-3-ethoxy)phenyl-2-(cyanomethyl)propenoate (11c). Reaction time: 20 minutes; oil; yield: 69%; ir (neat): 2250, 1712 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (t, 3 H, J = 7.0 Hz), 3.28 (s, 2 H), 3.86 (s, 3 H), 4.14 (q, 2 H, J = 7.0 Hz), 5.03 (s, 2 H), 6.82-7.24 (m, 3 H), 7.28-7.33 (m, 5 H), 7.85 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 14.9, 17.2, 52.5, 64.4, 75.2, 114.9, 117.5, 120.8, 122.4, 124.5, 128.2, 128.3, 129.0, 136.8, 140.8, 145.8, 152.3, 166.0. *Anal*. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.53; H, 5.85; N, 3.70.

Methyl (*E*)-3-(2-Benzyloxy-5-methyl)phenyl-2-(cyanomethyl)propenoate (11d). Reaction time: 30 minutes; white solid; yield: 89%; mp: 79-81℃; ir (potassium bromide): 2250, 1713 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32 (s, 3 H), 3.46 (s, 2 H), 3.88 (s, 3 H), 5.12 (s, 2 H), 6.86-6.89 (m, 1 H), 7.11-7.16 (m, 2 H), 7.31-7.41 (m, 5 H), 8.09 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.4, 20.5, 52.6, 70.5, 112.9, 117.7, 121.8, 123.1, 127.1, 128.0, 128.6, 130.2, 130.5, 131.7, 136.6, 140.7, 154.5, 166.2. *Anal*. Calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.52; H, 5.85; N, 4.18.

Methyl (*E*)-3-(2-Benzyloxy-5-nitro)phenyl-2-(cyanomethyl)-propenoate (11e). Reaction time: 5 minutes; white solid; yield: 91%; mp: 113-115 ℃; ir (potassium bromide): 2253, 1714 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.47 (s, 2 H), 3.91 (s, 3 H), 5.29 (s, 2 H), 7.07-7.10 (m, 1 H), 7.39-7.44 (m, 5 H), 7.99 (s, 1 H), 8.18-8.19 (m, 1 H), 8.24-8.28 (m, 1 H); ^{13}C nmr (deuterio-

chloroform): δ 17.2, 52.9, 71.3, 112.5, 116.5, 123.8, 124.8, 125.4, 126.9, 127.1, 128.7, 128.9, 134.8, 137.8, 141.3, 161.0, 165.5. *Anal*. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.59; H, 4.72; N, 7.69.

Methyl (*E*)-3-(2-Benzyloxy-3,5-dichloro)phenyl-2-(cyanomethyl)propenoate (11f). Reaction time: 15 minutes; oil; yield: 71%; ir (potassium bromide): 2252, 1718 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.25 (s, 2 H), 3.87 (s, 3 H), 4.96 (s, 2 H), 7.12 (d, 1 H, J = 2.5 Hz), 7.28-7.36 (m, 5 H), 7.49 (d, 1 H, J = 2.5 Hz), 7.63 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.1, 52.8, 76.3, 116.5, 124.6, 127.6, 128.5, 128.8, 129.2, 130.0, 130.1, 131.2, 131.5, 135.4, 138.2, 151.3, 165.3. *Anal*. Calcd. for $C_{19}H_{15}Cl_2NO_3$: C, 60.65; H, 4.02; N, 3.72. Found: C, 60.42; H, 4.15; N, 3.50.

Preparation of Methyl (*E*)-2-Cyanomethyl-3-(2-hydroxyphenyl)propenoates 12 : General procedure. To a stirred solution of **11** (1 mmole) in anhydrous dichloromethane (10 ml) was added boron trifluoride etherate (1.23 ml, 10 mmoles) and dimethyl sulfide (4.44 ml, 60 mmoles) at room temperature. After stirring for 2-24 hours under nitrogen atmosphere, the mixture was diluted with aqueous ammonium hydroxide (0.1 M, 20 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **12** as a solid.

The physical and spectral data of **12** prepared by this general method follows.

Methyl (*E*)-2-Cyanomethyl-3-(2-hydroxyphenyl)propenoate (12a). Reaction time: 5 hours; white solid; yield: 68%; mp: 101-103.5 ℃; ir (potassium bromide): 3334, 2257, 1707 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.47 (s, 2 H), 3.90 (s, 3 H), 6.27 (s, 1 H), 6.88-7.02 (m, 2 H), 7.24-7.31 (m, 2 H), 8.04 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.5, 52.8, 116.2, 117.6, 120.8, 120.9, 122.1, 129.9, 131.4, 140.5, 154.1, 166.5. *Anal*. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.11; H, 4.88; N, 6.29.

Methyl (*E*)-3-(5-Bromo-2-hydroxy)phenyl-2-(cyanomethyl)propenoate (12b). Reaction time: 12 hours; white solid; yield: 83%; mp: 150-152 ℃; ir (potassium bromide): 3396, 2254, 1692 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.59 (s, 2 H), 3.82 (s, 3 H), 6.90-6.93 (m, 1 H), 7.40-7.46 (m, 2 H), 7.82 (s, 1 H), 10.59 (br s, 1 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 16.9, 52.6, 110.1, 117.9, 118.0, 122.5, 122.7, 131.7, 133.7, 137.9, 155.2, 165.8. *Anal*. Calcd. for $C_{12}H_{10}BrNO_3$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.62; H, 3.43; N, 4.65.

Methyl (*E*)-2-Cyanomethyl-3-(3-ethoxy-2-hydroxy)phenylpropenoate (12c). Reaction time: 2 hours; white solid; yield: 65%; mp: 148.5-150 ℃; ir (potassium bromide): 3356, 2254, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (t, 3 H, J = 7.0 Hz), 3.48 (s, 2 H), 3.89 (s, 3 H), 4.15 (q, 2 H, J = 7.0 Hz), 6.11 (s, 1 H), 6.86-6.91 (m, 3 H), 8.03 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 14.8, 17.6, 52.6, 64.8, 112.6, 117.6, 120.0, 121.3, 122.4, 128.7, 139.4, 144.2, 146.0, 166.2. *Anal*. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.13; H, 5.55; N, 5.12.

Methyl (*E*)-2-Cyanomethyl-3-(2-hydroxy-5-methyl)phenylpropenoate (12d). Reaction time: 10 hours; white solid; yield: 75%; mp: 113.5-115 ℃; ir (potassium bromide): 3380, 2256, 1710 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3 H), 3.46 (s, 2 H), 3.89 (s, 3 H), 6.00 (s, 1 H), 6.76-6.80 (m, 1 H), 7.03-7.09 (m, 2 H), 8.00 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.6, 20.5, 52.7, 116.1, 117.6, 120.7, 122.2, 130.1, 130.2, 132.0, 140.5, 151.7, 166.5. *Anal*. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.35; H, 5.46; N, 5.79.

Methyl (*E*)-2-Cyanomethyl-3-(2-hydroxy-5-nitro)phenylpropenoate (12e). Reaction time: 10 hours; pale yellow solid; yield: 76%; mp: 169-172 ℃; ir (potassium bromide): 3221, 2266, 1705 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.64 (s, 2 H), 3.84 (s, 3 H), 7.10-7.13 (m, 1 H), 7.86 (s, 1 H), 8.16-8.23 (m, 2 H), 11.88 (br s, 1 H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 16.9, 52.7, 116.2, 117.8, 121.1, 123.8, 125.9, 127.0, 137.2, 139.4, 161.9, 165.6. *Anal*. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 54.72; H, 3.79; N, 10.43.

Methyl (*E*)-2-Cyanomethyl-3-(3,5-dichloro-2-hydroxy)phenylpropenoate (12f). Reaction time: 4 hours; white solid; yield: 73%; mp: 129-132 ℃; ir (potassium bromide): 3280, 2272, 1720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.44 (s, 2 H), 3.91 (s, 3 H), 5.95 (s, 1 H), 7.18 (d, 1 H, J = 2.4 Hz), 7.42 (d, 1 H, J = 2.4 Hz), 7.88 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 17.5, 52.9, 116.7, 121.4, 123.0, 124.8, 125.8, 128.2, 129.8, 137.5, 148.0, 165.5. *Anal*. Calcd. for $C_{12}H_9Cl_2NO_3$: C, 50.38; H, 3.17; N, 4.90. Found: C, 50.15; H, 3.06; N, 4.69.

Preparation of Methyl 2-Oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates 13: General Procedure. A stirred solution of **12** (1 mmole) and *para*-toluenesulfonic acid monohydrate (0.38 g, 2 mmoles) in toluene (5 ml) was heated at reflux temperature for 0.5-8 hours. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium bicarbonate solution (5 ml) and extrated with dichloromethane (3 × 10 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **13** as a solid.

The physical and spectral data of **13** prepared by this general method follows.

Methyl 2-Oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (13a). Reaction time: 2 hours; white solid; yield: 78%; mp: 84.5-86.5 ℃; ir (potassium bromide): 1770, 1699 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.45 (s, 2 H), 3.89 (s, 3 H), 7.27-7.52 (m, 4 H), 7.89 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 33.2, 52.7, 121.4, 124.8, 125.1, 125.6, 130.9, 131.4, 137.7, 150.7, 165.0, 167.7. *Anal*. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.87; H, 4.48.

Methyl 7-Bromo-2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (13b). Reaction time: 1 hour; white solid; yield: 76%; mp: 112-114 ℃; ir (potassium bromide): 1771, 1714 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.45 (s, 2 H), 3.89 (s, 3 H), 7.16-7.19 (m, 1 H), 7.57-7.60 (m, 2 H), 7.80 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 33.2, 52.9, 117.9, 123.3, 126.1, 127.4, 133.2, 134.2, 136.3, 149.7, 164.6, 166.9. *Anal*. Calcd. for $C_{12}H_9BrO_4$: C, 48.51; H, 3.05. Found: C, 48.39; H, 2.89.

Methyl 9-Ethoxy-2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (13c). Reaction time: 8 hours; pale yellow solid; yield: 61%; mp: 88-90 ℃; ir (potassium bromide): 1767, 1713 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (t, 3 H, J = 7.0 Hz), 3.44 (s, 2 H), 3.88 (s, 3 H), 4.13 (q, 2 H, J = 7.0 Hz), 6.90-7.05 (m, 2 H), 7.17-7.22 (m, 1 H), 7.86 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 14.7, 33.5, 52.7, 64.9, 114.6, 121.7, 125.1, 125.3, 126.9, 137.8, 140.5, 150.1, 165.0, 167.7. *Anal*. Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.38. Found: C, 63.90; H, 5.41.

Methyl 7-Methyl-2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (13d). Reaction time: 30 minutes; pale yellow

solid; yield: 87%; mp: 103-104.5 ℃; ir (potassium bromide): 1761, 1716 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.39 (s, 3 H), 3.43 (s, 2 H), 3.88 (s, 3 H), 7.16-7.29 (m, 3 H), 7.84 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 20.6, 33.2, 52.7, 121.2, 124.6, 125.3, 130.9, 132.2, 134.8, 137.8, 148.8, 165.1, 167.9. *Anal*. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.05; H, 5.18.

Methyl 7-Nitro-2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (13e). Reaction time: 1 hour; white solid; yield: 50%; mp: 149-152 ℃; ir (potassium bromide): 1783, 1716cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.51 (s, 2 H), 3.92 (s, 3 H), 7.43-7.46 (m, 1 H), 7.93 (s, 1 H), 8.32-8.39 (m, 2 H); ^{13}C nmr (deuteriochloroform): δ 33.4, 53.1, 122.9, 126.0, 126.2, 126.7, 127.2, 135.8, 144.3, 154.2, 164.3, 165.4. *Anal*. Calcd. for $C_{12}H_9NO_6$: C, 54.76; H, 3.45; N, 5.32. Found: C, 54.51; H, 3.22; N, 5.49.

Methyl 7,9-Dichloro-2-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (13f). Reaction time: 1 hour; white solid; yield: 63%; mp: 139-142 ℃; ir (potassium bromide): 1786, 1717cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.46 (s, 2 H), 3.90 (s, 3 H), 7.33 (d, 1 H, J = 2.4 Hz), 7.58 (d, 1 H, J = 2.4 Hz), 7.79 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 33.3, 53.0, 127.0, 127.7, 128.2, 128.5, 130.3, 131.5, 135.8, 145.0, 164.4, 166.0. *Anal*. Calcd. for $C_{12}H_8Cl_2O_4$: C, 50.20; H, 2.81. Found: C, 50.02; H, 2.64.

3-Cyanomethylcoumarin (16). To a stirred solution of **12a** (0.22 g, 1 mmole) in methanol (3 ml) was added sodium methoxide (0.065 g, 1.2 mmoles) and refluxed for 24 hours. The reaction mixture was neutralized with 5% aqueous hydrochloric acid solution (5 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent was evaporated *in vacuo*. The resulting mixture was chromatographed on silica gel eluting with hexane/ethyl acetate (3:1) to produce **16** as a yellow solid after crystallization with cold methanol, along with the recovery of starting compound **12a** (25%); mp: 166-168 ℃; ir (potassium bromide): 2260, 1715 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.71 (d, 2 H, J = 1.5 Hz), 7.32-7.39 (m, 2 H), 7.56-7.62 (m, 2 H), 7.96 (s, 1 H); ^{13}C nmr (deuteriochloroform): δ 19.5, 116.0, 116.7, 118.4, 118.7, 124.9, 128.0, 132.3, 140.6, 153.4, 160.1. *Anal*. Calcd. for $C_{11}H_7NO_2$: C, 71.35; H, 3.81; N, 7.56. Found: C, 71.12; H, 3.75; N, 7.33.

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REFERENCES AND NOTES

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[1a] For reviews of the Baylis-Hillman reaction, see: Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653. [b] Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. [c] Ciganek, E. *Org. React*. **1997**, *51*, 201. [d] Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049. [e] Basavaiah, D.; Rao, A. J.; Santyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. [f] Kataoka, T.; Kinoshita, H. *Eur. J. Org. Chem.* **2005**, 45. [g] Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511.

[2a] Song, Y. S.; Lee, C. H.; Lee, K.-J. *J. Heterocycl. Chem.* **2003**, *40*, 939. [b] Lee, C. H.; Song, Y. S.; Cho, H. I.; Yang, J. W.; Lee, K.-J. *J. Heterocycl. Chem.* **2003**, *40*, 1103. [c] Ko, S. H.; Lee, K.-J. *J. Heterocycl. Chem.* **2004**, *41*, 613. [d] Lee, C. H.; Lee, K.-J. *Synthesis* **2004**, 1941. [e] Hong, W. P.; Lee, K.-J. *Synthesis* **2005**, 33. [f] Hong, W. P.; Lee, K.-J. *Synthesis* **2006**, 963. [g] Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. *Synthesis* **2006**, 1953. [h] Lim, H. N.; Ji, S.-H; Lee, K.-J. *Synthesis* **2007**, 2454. [i] Song, Y. S.; Lee, K.-J. *Synthesis* **2007**, 3037. [j] Cha, M. J.; Song, Y. S.; Han, E.-G.; Lee, K.-J. *J. Heterocycl. Chem.* **2008**, *45*, 235. [k] Jeon, K. J.; Lee, K.-J. *J. Heterocycl. Chem.* **2008**, *45*, 615.

[3] Lim, H. N.; Song, Y. S.; Lee, K.-J. *Synthesis* **2007**, 3376.

[4a] Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans 1*, **2000**, 1331. [b] Kaye, P. T.; Robinson, R. S. *S. Afr. J. Chem.* **1998**, *51*, 47. [c] Kaye, P. T.; Robinson, R. S. *Synth. Commun.* **1996**, *26*, 2085.

[5a] Singh, V.; Pathak, R.; Batra, S. *Catal. Commun.* **2007**, *8*, 2054 [b] Yadav, J. S.; Gupta, M. K.; Pandey, S. K.; Reddy, B. V. S.; Sarma, A. V. S. *Tetrahedron Lett.* **2005**, *46*, 655. [c] Hong, W. P.; Lim, H. N.; Park, H. W.; Lee, K.-J. *Bull. Korean Chem. Soc.* **2005**, *26*, 655.

[6a] Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661. [b] Williard, P. G.; Fryhle, C. B. *Tetrahedron. Lett.* **1980**, *21*, 3731.

[7a] Pinner, A.; Klein, F. *Ber.* **1877**, *10*, 1889. [b] Pinner, A.; Klein, F. *Ber.* **1878**, *11*, 1475. [c] Aplander, K.; Hidestål, O.; Katebzadeh, K.; Lindström, U. M. *Green Chem.* **2006**, *8*, 22. [d] Kwok, R.; Wolff, M. E. *J. Org. Chem.* **1963**, *28*, 423.

[8a] Engler, A.; Anke, T.; Sterner, O. *J. Antibiot.* **1997**, *50*, 330. [b] Ishikawa, N. K.; Yamaji, K.; Tahara, S.; Fukushi, Y.; Takahasio, K. *Phytochemistry* **2000**, *54*. 777. [c] Marriott, K.-S.; Anderson, M.; Jackson, Y. A. *Heterocycles* **2001**, *55*, 91; [d] Tersawa, K.; Hosoya, H.; Sugita, Y.; Yokoe, I.; Sakagami, H. *Anticancer Res.* **2000**, *20*, 2951.

[9] Rizzacasa, M. A.; Sargent, M. V. *Aust. J. Chem.* **1987**, *40*, 1737.

[10] Ali, B. E.; Okuro, K.; Vasapollo, G.; Alper, H. *J. Am. Chem. Soc.* **1996**, *118*, 4264.

[11] Yoneda, E.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459.

[12] Rayabarapu, D. K.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 5630.

[13a] Murakami, M.; Tsuruta, T.; Ito, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 2484. [b] Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086.

[14] Fűrstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S.P. *J. Org. Chem.* **2000**, *65*, 2204.

[15] Thomas, D. H.; Gregory, P. R. *J. Org. Chem.* **1979**, *44*, 12, 2004.

[16] Rainford, L. C.; Tanzer, L. K. *J. Org. Chem.* **1941**, *6*, 722.

[17] Profit, E. *J. Prakt. Chem.* **1957**, 5, 175. *Chem. Abstr*. **1958**, *52*, 10940d.

[18] Chen, Han.; Fan, Y.-H.; Natarajan, A.; Guo, Y.; Iyasere, J.; Harbinski, F.; Luus, L.; Christ, W.; Aktas, H.; Halperin, J. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5401.

[19] Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807.

[20] Kaye, P. T.; Musa, M. A. *Synth. Commun.* **2003**, *33*, 1755.

[21] Colson, P.-j.; Awasthi, A. K.; Nagarajan, S. R. WO 9,944,985, 1999; *Chem. Abstr*. **1999**, *131*, 185252.