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Francis A. J. Kerdesky [a], Anthony Haight [a], B. A. Narayanan [a], Carl W. Nordeen [a], David Scarpetti [a], Louis S. Seif [a], Steven Wittenberger [a] & Howard E. Morton [a]

[a] Process Research, Department 45L, Pharmaceutical Products Division Abbott Laboratories, Abbott Park, Illinois, 60064

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AN EFFICIENT SYNTHESIS OF AN ANGIOTENSIN II ANTAGONIST (A-81988)

Francis A. J. Kerdesky* , Anthony Haight[1], B. A. Narayanan[1], Carl W. Nordeen, David Scarpetti[1], Louis S. Seif, Steven Wittenberger and Howard E. Morton*

Process Research, Department 45L, Pharmaceutical Products Division
Abbott Laboratories, Abbott Park, Illinois 60064

ABSTRACT: A new and efficient synthesis of A-81988, an angiotensin II antagonist, is described. The preparation utilizes a novel method for tetrazole formation from nitriles requiring trimethylsilyl azide and a catalytic amount of dialkyltin oxide.

Nonpeptide angiotensin II (AII) receptor antagonists are currently being investigated for the treatment of various cardiovascular disorders, including hypertension.[2] A-81988 (**1**) has recently been reported to be a potent, orally active angiotensin II antagonist with a long duration of action whose pharmacological profile has established it as an important tool for the investigation of a variety of AII mediated pathological conditions.[3] The existing methodology for its preparation, however, is problematic on a large scale. Herein we present a novel, reliable and efficient synthesis of the compound which is amenable to large scale and analog preparation.

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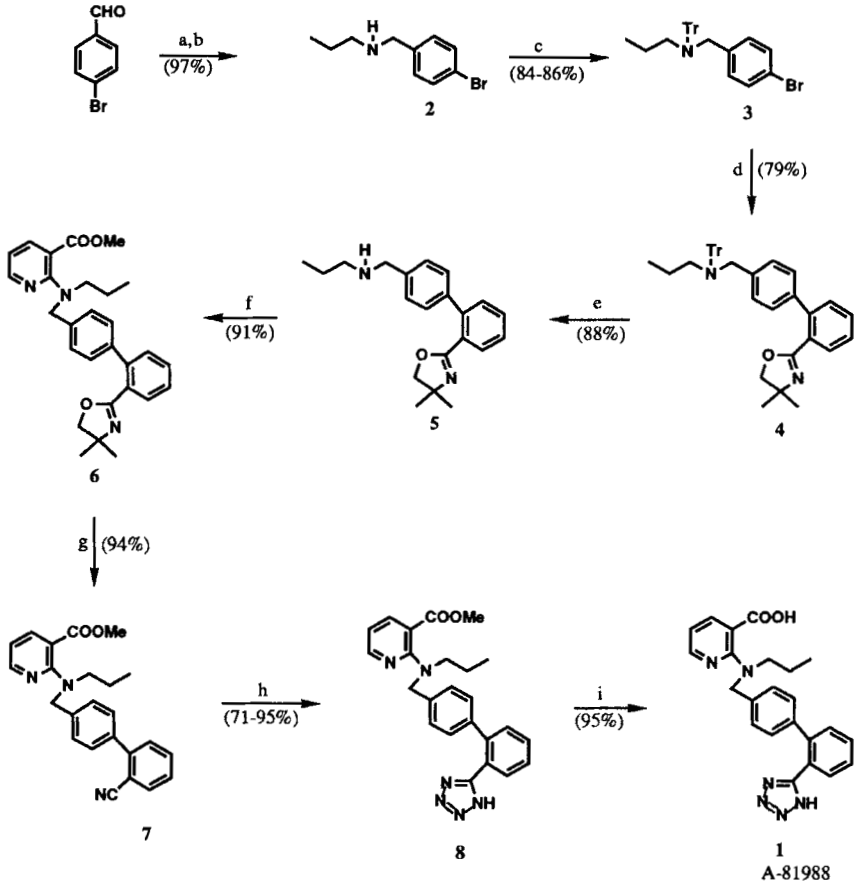
* To whom correspondence should be addressed.

The AII antagonist was prepared as delineated in Scheme I. 4-Bromobenzaldehyde was reacted with a methanolic solution of n-propylamine to form the Schiff base which was then reduced by catalytic hydrogenation to afford the secondary amine **2** in good yield. Typically 2-5% of undesired desbromo byproduct was also obtained under these reaction conditions. Alternatively, hydride reduction ($NaBH_4$) afforded the desired amine **2** in excellent yield and purity. The secondary amine **2** was treated with trityl chloride to provide the crystalline protected amine **3**. Tertiary amine **3** was converted to the corresponding Grignard reagent in refluxing tetrahydrofuran and subsequently reacted with 1-methoxy-2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)benzene[4] to afford protected biphenyl amine **4** as a white solid after crystallization from methanol. The trityl protecting group was readily removed by treatment with acetic acid to give propylamine **5** (57% overall from 4-bromobenzaldehyde).

Having established an efficient route to the biphenyl moiety, our attention turned to the alkylation of the secondary amine with methyl 2-chloronicotinate.[5] In this reaction, the choice of solvent, temperature and concentration was of paramount importance. Thus, treatment of **5** with methyl 2-chloronicotinate (1.3 equiv.) and triethylamine (3 equiv.) in refluxing toluene gave the desired coupling product **6** in high yield (91%). Lower temperatures (<100°C) and concentrations (<1M) generally gave inferior yields of product. Solvents such as toluene and xylene gave better results than tetrahydrofuran, methanol, or dimethylformamide.

Completion of the synthesis now required a reliable method for formation of the tetrazole ring. Oxazoline **6** was converted to the nitrile **7**

Scheme I



a. $PrNH_2$, MeOH b. H_2, Pd/C, MeOH or $NaBH_4$, EtOH, H_2O c. Trityl Cl, NEt_3, CH_2Cl_2
d. Mg, 1-Methoxy-2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)benzene, THF e. HOAc, CH_3OH, H_2O
f. Methyl 2-Chloronicotinate, NEt_3, $CH_3C_6H_5$ g. $POCl_3$, C_5H_5N h. Me_3SiN_3, Me_2SnO, $CH_3C_6H_5$ or $(CH_3)_3SnCl$, NaN_3, $CH_3C_6H_5$ i. NaOH, MeOH, Dioxane.

by exposure to phosphorous oxychloride at reflux in pyridine.[6] The known reaction of nitriles with hydroazoic acid[7], unfortunately, was judged too hazardous for our large scale work. Therefore we chose to explore the utility of various "tin azide" combinations. Gratifyingly, treatment of nitrile **7** with trimethylsilyl azide in the presence of a catalytic amount of dimethyltin oxide (dibutyltin oxide gave similar results) at approximately 95°C afforded the tetrazole **8** in 71% yield. This transformation was also accomplished in 85% yield utilizing trimethyltin azide.[8] Although the latter method gave a higher yield, the use of the catalytic tin method[9] was preferred because it eliminated the possibility of exposure to the volatile, noxious and toxic trialkyltin chloride used for the preparation of trialkyltin azide.[10] When a stoichiometric amount of dibutyltin oxide was utilized, yields greater than 90% were obtained. The synthesis was completed by hydrolyzing the methyl ester of tetrazole **8** to the acid **1** (A-81988) by treatment with sodium hydroxide. The product was identical in all respects (spectral and analytical) to that prepared by the earlier route.[3]

In summary, we have developed a novel and efficient synthesis of A-81988, an AII antagonist. The chemistry described is amenable to large scale and is flexible enough to allow for the preparation of analogs. In addition, the methodology developed requires no chromatography. The intermediates are in some cases of sufficient purity to be used in the next step or can be purifed by recrystallization. Finally, the synthesis helps to establish the use of trimethylsilyl azide / dialkyltin oxide as a new and less hazardous alternative for tetrazole formation.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Melting points are uncorrected and were measured with a Thomas-Hoover Unimelt apparatus. ^{1}H NMR spectra were obtained on a General Electric QE-300 NMR instrument at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^{1}H NMR data are tabulated in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were recorded with an HP5985A spectrometer. Merck TLC plates were used for analytical TLC and Merck Kieselgel 60 was used for column chromatography. Microanalyses were performed by the Abbott Analytical Department.

N-(4-Bromophenylmethyl)-N-propylamine (2). To 4-bromobenzaldehyde (100 g, 0.54 mol) and n-propylamine (36.3 g, 0.60 mol) in methanol (100 mL) was added 5% platinum on carbon (1.00 g). This mixture was shaken in a Paar hydrogenation reactor overnight to complete formation of the Schiff base. The reaction was then hydrogenated under 4 atmospheres of hydrogen until the theoretical uptake of hydrogen had been consumed. The catalyst was removed by filtration through a 0.45 μ nylon frit and washed with methanol. The filtrate was concentrated under reduced pressure and the residue obtained dissolved in ether (500 mL). The ether solution was washed with water (2 X 100 mL), 10% sodium bicarbonate solution (2 X 100 mL), and water (2

X 100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford **2** (121.34 g). GC-MS showed this material to be 98.5% pure product containing 1.5% of the desbromo compound; the yield is 96.93% based on the GC purity of the product obtained. An analytical sample was prepared by distillation (130-150°C, 0.18 Torr). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 9 Hz, 2H), 7.20 (d, J = 9 Hz, 2H), 3.74 (s, 2H), 2.57 (t, J = 7.4 Hz, 2H), 1.53 (tq, $J_1 = J_2$ = 7.4 Hz, 2H), 1.36 (bs, 1H), 0.92 (t, J = 7.4 Hz, 3H); MS (DCI/NH_3) *m/e* 230 $(M+H)^+$. Anal. Calcd for $C_{10}H_{14}BrN$: C, 52.44; H, 6.18; N, 6.14. Found: C, 53.12; H, 6.24; N, 6.18.

N-(4-Bromophenylmethyl)-N-propylamine-N-tritylamine(3). (Method A) To a stirred solution of **2** (49.7 g, 0.218 mol) dissolved in methylene chloride (500 mL) under nitrogen at 0°C was added triethylamine (36 mL), followed by trityl chloride (63.8 g, 0.229 mol). The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 18 h. The resultant slurry was diluted with methylene chloride (1 L) and washed with water (2 X 100 mL), 10% aqueous sodium bicarbonate (100 mL) and brine (100 mL). Drying ($MgSO_4$) and concentrating under reduced pressure gave a pale yellow oil. Crystallization from ethanol (500 mL) afforded **3** as a white solid (103 g, 84%), mp 136-137°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 7.5 Hz, 2H), 7.45 (s, 4H), 7.27 (dd, J = 7.5 Hz, 6H), 7.17 (bdd, $J_1 = J_2$ = 7.5 Hz, 3H), 3.57 (s, 2H), 2.24 (m, 2H), 0.95 (m, 2H), 0.47 (bt, J = 7.5 Hz, 3H). Anal. Calcd for $C_{29}H_{28}BrN$: C, 74.04; H, 6.00; N, 2.98. Found: C, 73.74; H, 5.92; N, 2.92.

(Method B) 4-Bromobenzaldehyde (92 g, 0.5 mol) was dissolved in ethanol (400 mL) and cooled to 5°C. Propylamine (66 mL, 0.8 mol) in water (70 mL) was added and the mixture stirred at 23°C for 2 h. Sodium borohydride (13 g, 0.35 mol) was then added portionwise and the temperature maintained at 55°C for 1 h. The contents were concentrated in vacuo and ethyl acetate (0.5 L) was added. The mixture was filtered and the filtrate was washed with water and dried. The organic phase was concentrated in vacuo to yield a liquid amine which was dissolved in methylene chloride (0.5 L). A solution of trityl chloride (144 g, 0.52 mol) in methylene chloride (500 mL) was added followed by the addition of a solution of triethylamine (104 ml, 0.72 mol) in methylene chloride (60 mL). The resulting suspension was then stirred for 12 h at 23°C. The reaction was terminated by the addition of water (350 mL). The organic phase was separated and washed with 10% brine (350 mL) and water (350 mL). The organic phase was concentrated in vacuo to give an orange oil which was crystallized from isopropyl alcohol to provide **3** (200 g, 86%).

N-[2'-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-yl-methyl]-N-propyl-N-tritylamine (4). To a solution of **3** (47.0 g, 0.1 mol) dissolved in anhydrous tetrahydrofuran (300 mL) at ambient temperature under nitrogen was added magnesium turnings (2.55 g, 0.105 mol). The reaction mixture was heated to reflux at which time 1,2-dibromoethane (0.43 mL) was added to initiate Grignard formation. After refluxing for 6 h the reaction mixture was cooled to ambient temperature and 1-methoxy-2-(4,4-dimethyl-4,5-dihydro-oxazol-2-yl)benzene[4] (21.54

g, 0.105 mol) was added in one portion. The reaction mixture was allowed to stir at ambient temperature overnight and then quenched by the addition of saturated aqueous ammonium chloride (300 mL) and diluted with ethyl acetate (700 mL). The organic layer was separated, washed with 5 % sodium hydrogen sulfate, water, 5% aqueous sodium bicarbonate and brine, dried ($MgSO_4$) and concentrated under a reduced pressure to give a yellow oil. The crude product was crystallized from methanol (200 mL) to give 44.5 g (79%) of **4**, mp 151-153°C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 7.5 Hz, 6H), 7.56 (d, J = 7.5 Hz, 2H), 7.48 (ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 7.33-7.45 (m, 4H), 7.29 (dd, J = 7.2 Hz, 7.5 Hz, 6H), 7.18 (dd, $J_1 = J_2$ = 7.2 Hz, 3H), 3.79 (s, 2H), 3.64 (bs, 2H), 2.27 (m, 2H), 1.32 (s, 6H), 0.94-1.08 (m, 2H), 0.48 (t, J = 7.5 Hz, 3H); MS (DCI/NH_3) *m/e* 564 $(M+H)^+$. Anal. Calcd for $C_{40}H_{40}N_2O$: C, 85.06; H, 7.14; N, 4.96. Found: C, 85.41; H, 7.09; N, 4.84.

N-[2'-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-yl-methyl]-N-propylamine (5). Compound **4** (21.0 g, 37.0 mmol) dissolved in methanol (16 mL), water (16 mL) and acetic acid (16 mL) was stirred at reflux for 2 h. The reaction mixture was allowed to cool to ambient temperature and then the methanol was removed under reduced pressure. Ethyl acetate (500 mL) and 1N hydrochloric acid (50 mL) were added. The aqueous layer was separated and the organic layer extracted with 1N HCl (10 mL). The combined aqueous extracts were washed with ethyl acetate (100 mL), basified with 2N sodium hydroxide (45 mL) and extracted with ethyl acetate (3 X 200 mL). The

combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give **5** (11.91 g, 88%) as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (bd, J = 7.8 Hz, 1H), 7.47 (m, 1H), 7.31-7.42 (bm, 6H), 3.84 (s, 2H), 3.80 (s, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.56 (m, 3H), 1.30 (s, 6H), 0.94 (t, J = 7.5 Hz, 3H); MS (DCI/NH_3) *m/e* 323 $(M+H)^+$. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.21 ; H, 8.13; N, 8.69. Found: C, 78.42; H, 8.18; N, 8.65.

Methyl 2-{N-Propyl-N-[(2'-[4,4-dimethyl-4,5-dihydro-oxazol-2-yl]biphenyl-4-yl)methyl]amino}pyridine-3-carboxylate (6). The propylamine **5** (32.2 g, 0.1 mol), triethylamine (30.3 g, 0.3 mol), and methyl 2-chloronicotinate[5] (22.2 g, 0.13 mmol) were dissolved in toluene (100 mL). The reaction mixture was heated to reflux and monitored by TLC. (Reaction rate varies according to amount of starting material). After 40 hours, the reaction mixture was cooled to 23°C and partitioned between ethyl acetate (500 mL) and saturated sodium bicarbonate (500 mL). The organic layer was dried ($MgSO_4$) and removed in vacuo to afford a crude residue which filtered through a pad of silica (ethyl acetate/ hexane : 1/3) to give **6** as a viscous, colorless oil (41.59 g, 91%). ^1H NMR (300 MHz, $CDCl_3$): δ 8.35 (m, 1H), 7.91 (m, 1H), 7.75 (m, 1H), 7.45-7.52 (m, 1H), 7.35-7.40 (m, 5H), 6.69 (dd, 1H, J = 7.5 Hz), 4.70 (s, 2H), 3.82 (s, 3H), 3.79 (s, 2H), 3.29 (t, 2H, J = 7.5 Hz), 1.55-1.65 (m, 2H), 1.30 (s, 6H), 0.82 (t, 3H, J = 7 Hz); MS (DCI/NH_3) *m/e* 458 $(M+H)^+$. Anal. Calcd for $C_{28}H_{31}N_3O_3$: C, 73.48; H, 6.83; N, 9.19. Found: C, 73.62; H, 6.78; N, 9.22.

Methyl 2-{N-Propyl-N-[(2'-cyanobiphenyl-4-yl)methyl]amino}-pyridine-3-carboxylate (7). The oxazoline **6** (45 g, 0.1 mol) in pyridine (300 mL) was treated with phosphorous oxychloride (20 ml, 0.2 mol) then heated at 120°C for 2 h. After cooling to 10°C, ethyl acetate (1.5 L) was added and the reaction mixture washed with 1N NaOH (2 X 300 mL), water (300 mL), and brine (300 mL) and dried ($MgSO_4$). Filtration, concentration, and stripping from toluene (2 X 300 ml) gave a yellow oil which was filtered through a pad of silica (ethyl acetate/hexane : 1/3) and crystallized from cyclohexane to give **7** (36 g, 94%) as a white solid, mp 74-75°C. The ^1H NMR (300 MHz, $CDCl_3$): δ 8.28 (m 1H), 7.91 (m, 1H), 7.75 (m, 1H), 7.58-7.67 (m, 1H), 7.39-7.55 (m, 5H), 6.70 (dd, J_1 = J_2 = 7 Hz, 1H), 4.75 (s, 2H), 3.82 (s, 3H), 3.30 (t, 2H, J = 7 Hz), 1.53-1.68 (m, 2H), 0.82 (t, J = 7 Hz, 3H); MS (DCI/NH_3) *m/e* 386 $(M+H)^+$. Anal. Calcd for $C_{24}H_{23}N_3O_2$: C, 74.77; H, 6.02; N, 10.91. Found: C, 74.89; H, 5.97; N, 10.95.

Methyl 2-{N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)-methyl]amino}pyridine-3-carboxylate (8). (Method A) Trimethylsilyl azide (23 g, 0.2 mol) was added to a solution of the nitrile **7** (38.5 g, 0.1 mol) in toluene (500 mL) under nitogen. Dimethyltin oxide (1.64 g, 0.01 mol) was then added. The resulting suspension was then heated to approximately 95°C (mixture became homogeneous after heating) for 48 h. The mixture was cooled and washed successively with water, 5% aqueous HCl, and water. The first water wash was also extracted with methylene chloride. The organic layers were dried ($MgSO_4$) and the solvent removed. An alternative workup involved extracting the mixture

with 1N NaOH, acidifying the aqueous phase to pH 3-4, and extraction with methylene chloride and/or collection of the precipitate. The dried residue was recrystallized from ethyl acetate to give **8** (30.3 g, 71%) as a white solid, mp 146-147°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.22 (m, 1H), 7.83 (m, 1H), 7.61-7.69 (m, 2H), 7.51-7.60 (m, 2H), 7.21 (d, J = 7 Hz, 2H), 7.01 (d, J = 7 Hz, 2H), 6.76 (dd, $J_1 = J_2$ = 7 Hz, 1H), 4.69 (s, 2H), 3.82 (s, 3H), 3.19 (t, 2H, J = 7 Hz), 1.42-1.55 (m, 2H), 0.73 (t, J = 7 Hz, 3H). MS (DCI/NH_3) *m/e* 429 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}N_6O_2$: C, 67.26; H, 5.65; N, 19.62. Found: C, 67.15; H, 5.68; N, 19.57.

(Method B) A mixture of the nitrile **7** (100 g, 0.26 mol), trimethyltin chloride (59.7 g, 0.30 mol), sodium azide (19.4 g, 0.30 mol) in dry toluene (l L) was heated to reflux. After 70 h, the reaction mixture was allowed to cool. The solid was filtered and the toluene layer and solid residue were washed with water (2 X 100 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The dry solid residues were triturated with ether/hexane and dissolved in a solution of toluene/tetrahydrofuran (95/5, 500 mL) containing hydrogen chloride (19 g, 0.52 mol). After stirring for 2 h, the solvent was removed and the residue recrystallized from ethyl acetate to give **8** (94 g, 85%).

2-{N-Propyl-N-[(2'-[1H-tetrazol-5-yl]biphenyl-4-yl)methyl]-amino}pyridine-3-carboxylic acid (1). The methyl ester **8** (107 g, 0.25 mol) in 50% MeOH/dioxane (1.5 L) was treated with sodium hydroxide (51 g of reagent assayed as 98.1% pure, 1.25 mol) in water (100 mL) and heated at 50°C for 5 h. After cooling, the reaction mixture was acidified with 12N HCl (125 mL, 1.5 mol). The mixture was then

evaporated followed by washing with water and ethyl acetate. The dried crude residue was extracted with warm chloroform and partitioned between chloroform and water. The chloroform layers, after washing with water, were dried ($MgSO_4$) and the solvent removed to give a solid. The solid was washed throughly with ethyl acetate and dried to afford **1**[3] as a white crystalline solid (104 g, 95%), mp 199-200°C. ^1H NMR (300 MHz, DMSO-d_6): δ 13.21 (br s, 1H), 8.23 (m, 1H), 7.88 (m, 1H), 7.61-7.71 (m, 2H), 7.51-7.59 (m, 2H), 7.22 (d, J = 7 Hz, 2H), 7.01 (d, J = 7 Hz, 2H), 6.80 (dd, $J_1 = J_2$ = 7 Hz, 1H), 4.68 (s, 2H), 3.23 (t, J = 7 Hz, 2H), 1.42-1.55 (m, 2H), 0.73 (t, J = 7 Hz, 3H). MS (DCI/NH_3) *m/e* 415 $(M+H)^+$.

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REFERENCES

1. Process Research, Department 54P, Chemical and Agricultural Products Division, Abbott Laboratories, North Chicago, Illinois 60064

2. Duncia, J. V.; Carini, D. J.; Chiu, A. T.; Johnson, A. L.; Price, W. A.; Wong, P.C.; Wexler, R. R.; Timmermans, P. B. M. W. M. *Med. Res. Rev.* **1992**, *12*, 149.

3. De, B.; Winn, M.; Zydowsky, T. M.; Kerkman, D. J.; DeBarnardis, J. F.; Lee, J.; Buckner, S.; Warner, R.; Brune, M.; Hancock, A.; Opgenorth, T.; Marsh, K. *J. Med. Chem.* **1992**, *35*, 3714.

4. (a) Meyers, A. I., Mihelich, E. D.; *J. Am. Chem. Soc.* **1975**, *97*, 7383.
(b) Aldrich, P. E.; Duncia, J. V.; Pierce, M. E. U.S. Patent 4,870,186.

5. Mann, F. G.; Reid, J. A. *J. Chem. Soc.* **1952**, 2057.

6. Dordor, I. M.; Mellor, J. M. *Tetrahedron Lett.* **1983**, *24*, 1437.

7. Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc.* **1958**, *80*, 3908.

8. Luitjen, J. G.; Janssen, M. J.; Van Der Kirk, G. J. M. *Recl. Trav. Chim. Pays-Bas* **1963**, *81*, 286

9. Wittenberger, S. J.; Donner, B. G. Submitted .

10. The use of catalytic "tin" also minimizes the risk of residual tin in the reaction product. In general, tin residues can be removed either by recrystalization or silica gel chromatography.

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