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Synthetic Studies Towards ML-3000 A Concise Synthesis of This Non-Steroidal Anti-Inflammatory Drug

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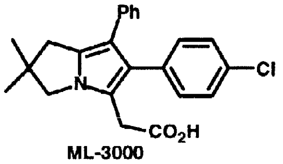
Abstract: ML-3000 was obtained from 1-chloro-3-phenyl-2-propyne in 8 steps with an overall yield of 19%. The key steps are a thermal acid-promoted bicyclization of an ω-acetylenic amino ester and a Suzuki cross-coupling reaction between a heteroaryl triflate and (4-chlorophenyl)boronic acid.

Non-steroidal antiinflammatory drugs (NSAIDs) are the main therapeutic agents for the treatment of the symptoms of arthritis. The drugs seem to inhibit the enzyme cyclooxygenase and consequently the conversion of arachidonic acid into prostaglandins.[1] The main drawbacks of NSAIDs are severe side effects including gastrointestinal ulceration and bronchospasm.[2]

Prostaglandins have been proven to be cytoprotective and antisecretory.[3] A decrease in the level of prostaglandins engendered by inhibition of cyclooxygenase disturbs this protective mechanism. A second hypothesis focuses on leukotrienes that are formed by the 5-lipoxygenase enzyme from arachidonic acid. Leukotrienes have been reported to play an important role in acidic gastrointestinal ulceration.[4] Inhibiting cyclooxygenase may increase the metabolism of arachidonic acid via the leukotriene pathway.[5] The search for compounds that inhibit both cyclooxygenase and 5-lipoxygenase is a challenge. Recently, 2,3-dihydro-1*H*-pyrrolizine derivatives such as ML-3000 have been proven to selectively inhibit the enzymes cyclooxygenase (IC_{50} = 0.21 μM) and 5-lipoxygenase (IC_{50} = 0.18 μM).[6, 7] Thus ML-3000 is one of the most potent and well-balanced dual inhibitor of both enzymes.[8] However, the previous synthesis of ML-3000 proceeds with poor overall yield (< 5%).[6]



ML-3000

Herein, we report a short and efficient synthesis of ML-3000 that features a thermal acid-promoted bicyclization of an ω-acetylenic amino ester. In a previous communication, we reported a convenient synthetic method that provides access to polysubstituted pyrrolidines based on a

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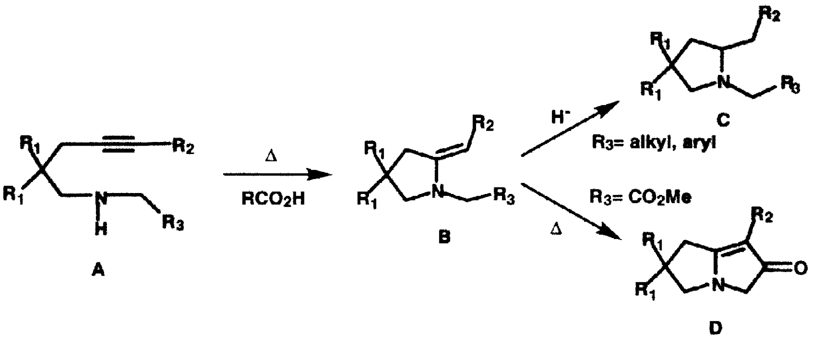
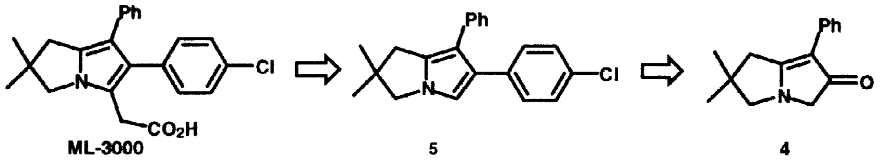
thermal cyclization of ω-acetylenic amines, via an enamine.[9] A smooth thermolysis of ω-acetylenic amines **A** in the presence of pivalic acid (1 equiv.) without solvent led to the cyclic enamines **B**, which could be reduced to the corresponding pyrrolidines **C**. Furthermore, we have reported an extension of this reaction, in which the enamine is trapped intramolecularly with an appropriate acceptor such as an ester group, providing an efficient synthesis of substituted 2,3,5,6-tetrahydro-6-oxo-1*H*-pyrrolizines **D**[10] (Scheme 1).

Scheme 1: Synthesis of pyrrolidines and 2,3,5,6-tetrahydro-6-oxo-1*H*-pyrrolizines



Due to a facile construction of tetrahydropyrrolizinones from ω-acetylenic amino esters, a formal synthesis of ML 3000 was planed from the bicyclic enaminone **4** via the known intermediate **5**[6] (Scheme 2).

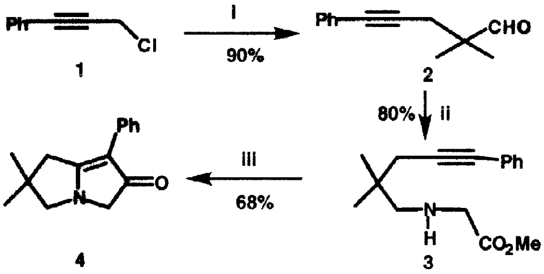
Scheme 2: Retrosynthesis of ML-3000



The ω-acetylenic amino ester **3** required for the synthesis of the 2,3-dihydro-1*H*-pyrrolizine skeleton of ML-3000 was obtained from 1-chloro-3-phenyl-2-propyne **1** in two steps.[11] Treatment of chloride **1** with isobutyraldehyde under basic phase transfer catalysis (cat. *n*-Bu_4NI, NaOH, H_2O, toluene, 50 °C)[12] in the presence of a catalytic amount of NaI produced the aldehyde **2** (90%). The condensation of aldehyde **2** with methyl glycinate hydrochloride under reductive amination by using $NaBH(OAc)_3$ in the presence of Et_3N,[13] furnished the ω-acetylenic amino ester **3** (80%). The thermolysis of the ω-acetylenic amino ester **3** at 150 °C, in the presence of pivalic acid (1 equiv.) without solvent, produced the tetrahydro-6-oxo-1*H*-pyrrolizine **4** in good yield (68%) (Scheme 3).

An attempt to transform the tetrahydro-6-oxo-1*H*-pyrrolizine **4** into **5** was achieved by addition of 4-chlorobenzene magnesium bromide to **4**. Unfortunately, the addition of 4-chlorobenzene magnesium bromide to the enaminone **4** without or with $CeCl_3$,[14] followed by acidic work up, did not allow the isolation of the dihydro-1*H*-pyrrolizine **5**. In these conditions, degradation products were observed.

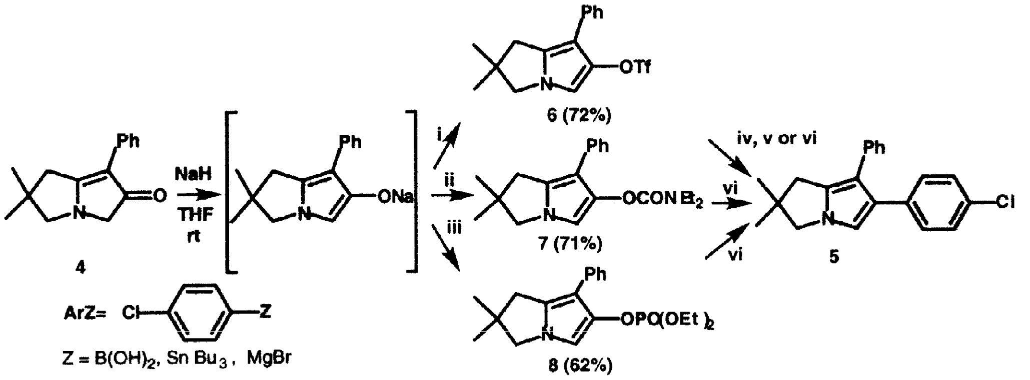
Scheme 3: Synthesis and thermolysis of ω-acetylenic amino ester 3



i - Isobutyraldehyde, cat n-Bu_4NI, cat. NaI, $NaOH/H_2O$/toluene, 50°C
ii - glycine methyl ester hydrochloride, $NaBH(OAc)_3$, Et_3N, CH_2Cl_2; rt
iii - 150 °C, t-$BuCO_2H$ (1 equiv.)

The introduction of the *p*-chlorophenyl group was also examined by using a cross-coupling reaction, e.g., heteroaryl triflate with organoboron,[15] organostannane,[16] or Grignard reagent,[17] as well as cross coupling reactions of heteroaryl carbamates[17] or phosphates[18] with Grignard reagents. The enone **4** was transformed into heteroaryl triflate **6**,[19] carbamate **7** and phosphate **8**. After treatment of **4** with NaH in THF, the sodium enolate was quenched with *N*-phenyltrifluoromethanesulfonimide, diethylcarbamyl chloride or diethyl chlorophosphate to produce respectively **6** (72%), **7** (71%) and **8** (62%). Compound **5** was isolated in low yield (< 10%) when the cross-coupling reaction of the enol triflate **6**, or the carbamate **7** or the enol phosphate **8** was performed with *p*-chlorobenzene magnesium bromide in the presence of a catalytic amount of $Ni(acac)_2$ in refluxing THF or at rt. When the cross-coupling reaction of the triflate **6** was achieved with *p*-chlorotributylstannylbenzene in the presence of a catalytic amount of $Pd(PPh_3)_4$ and LiCl (as the additive), in refluxing THF, no coupling product **5** was detected. However, **5** was obtained in only 15% yield when a Suzuki cross-coupling reaction, between the triflate **6** and (4-chlorophenyl)boronic acid, was achieved in the presence of $Pd(PPh_3)_4$ and 5.4 M KOH/H_2O in refluxing THF (Scheme 4). It seems that these low yields are the result of the low stability of compound **5** in the reaction conditions. Furthermore, we have noticed a degradation of **5** during its purification on silica gel.

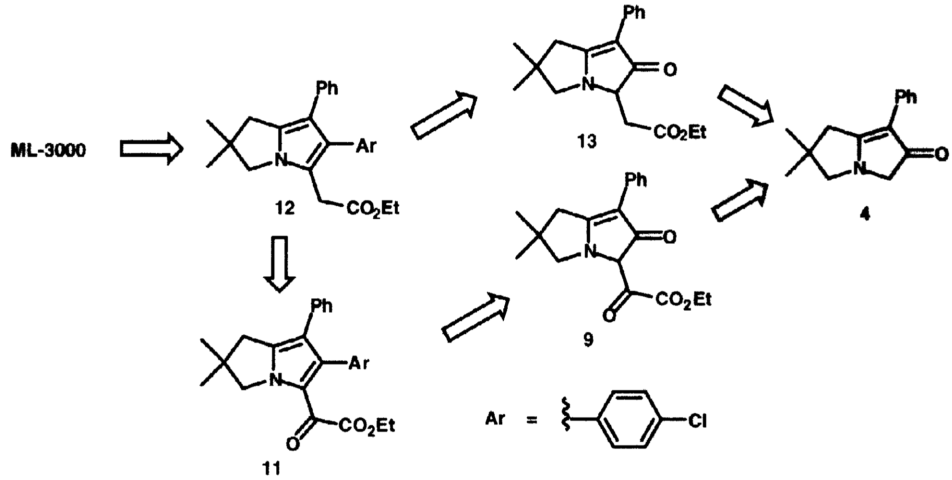
Scheme 4: Transformation of **4** into compound **5**



i - $PhNTf_2$, 0 °C to rt; ii - $ClCONEt_2$, 0 °C to rt; iii - $ClPO(OEt)_2$, 0 °C to rt; iv - $ArB(OH)_2$, cat $Pd(PPh_3)_4$, KOH/H_2O, reflux; v - $ArSnBu_3$, cat $Pd(PPh_3)_4$, LiCl, reflux; vi - ArMgBr, cat $Ni(acac)_2$, THF, rt or reflux.

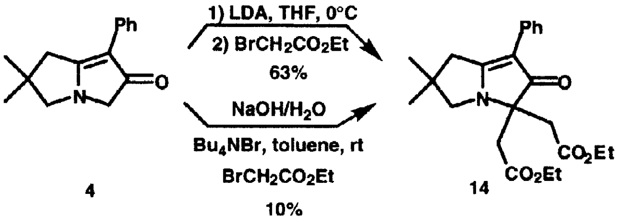
As the esters of ML 3000 are stable,[6, 20] it seems that 2,3,5,6-tetrahydro-6-oxo-*1H*-pyrrolizines are stabilized when the pyrrole ring is substituted by an acetic ester side chain. According to this observation, the synthesis of ML-3000 was planed from **12** via intermediate **13**, or from **11**, as an electron withdrawing group should have a better stabilizing effect on the pyrrole ring. Compound **11** could be synthesized from **4** via diketone **9** (Scheme 5).

Scheme 5: Second approach to ML-3000



Different conditions were tried to transform enone **4** into the monoalkylated product **13**. When **4** was treated with LDA (1.3 equiv) in THF at 0 °C, followed by the addition of ethyl bromoacetate (1.5 equiv.) at 0°C or -78°C, the monoalkylated product **13** was not observed, but the dialkylated compound **14** was isolated in 63% yield. Under phase transfer catalysis (NaOH/H_2O, toluene, cat. Bu_4NBr, rt), the dialkylated product, which was also the only isolable product, was obtained in poor yield (10%) (Scheme 6).

Scheme 6: Alkylation of **4**

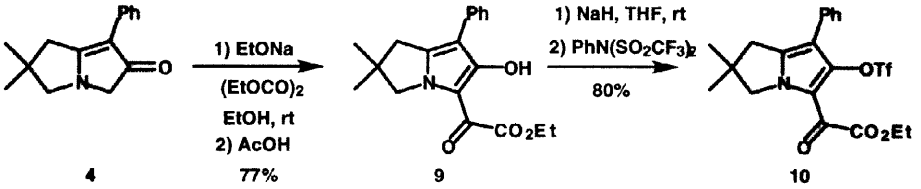


Due to these results, the synthesis of ML-3000 was planed from diketone **9**. The α-ketoester side chain was introduced by acylation of the tetrahydro-6-oxo-1*H*-pyrrolizine **4** with diethyl oxalate under basic conditions (EtONa, EtOH, rt).[21] The resulting β-diketone **9** (77%) was entirely enolized, and this product was stable (Scheme 7). The introduction of the *p*-chlorophenyl group was achieved by using a Suzuki cross-coupling reaction[15] (Scheme 8).

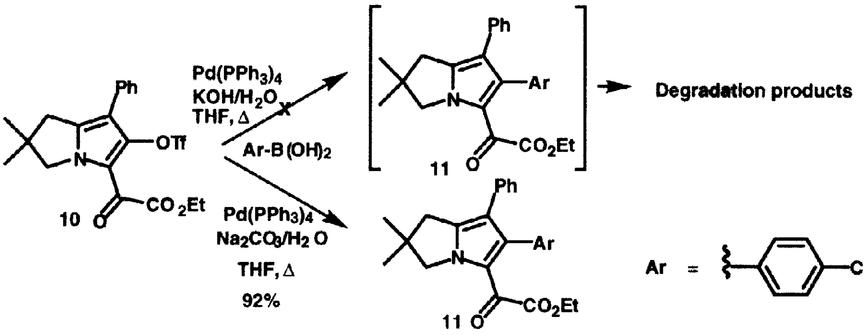
After treatment of **9** with *N*-phenyltrifluoromethanesulfonimide under basic conditions (NaH, THF, rt, 80%)[19] (Scheme 7), the resulting triflate **10** was tentatively coupled with

(4-chlorophenyl)boronic acid in the presence of $Pd(PPh_3)_4$ (0.05 equiv.) and KOH/H_2O (5.4 M) in refluxing THF. In these conditions, **11** was not detected but degradation compounds were formed probably due to the sensitivity of the ketoester moiety to the strongly basic conditions. According to this result, the Suzuki reaction was performed under milder basic conditions by using Na_2CO_3/H_2O in refluxing THF. In these conditions, the desired product **11** was obtained in 92% yield (Scheme 8).

Scheme 7: Transformation of **4** into the enol triflate **10**

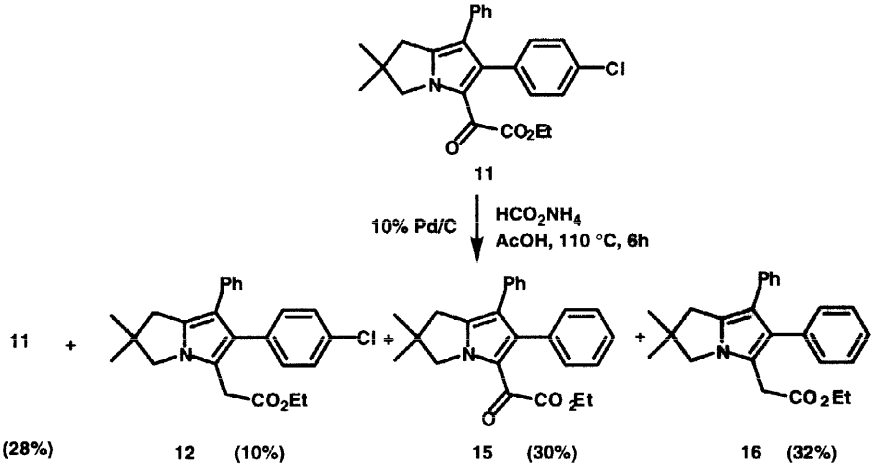


Scheme 8: Suzuki coupling



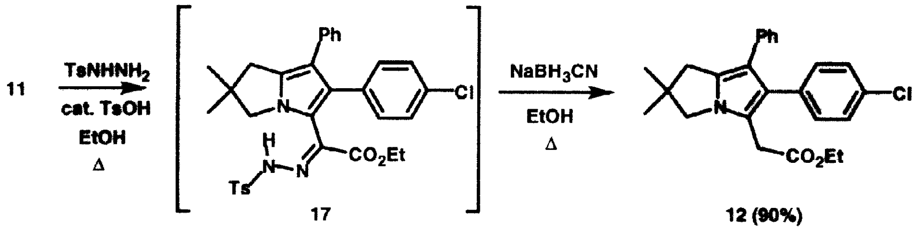
The reduction of ketoester **11** into **12**, with ammonium formate (HCO_2NH_4) in the presence of 10% Pd/C in AcOH at 110 °C[22] led to four unseparated products in the crude reaction mixture, **11** (starting material), **12**, **15**, **16** in a ratio of 28%, 10%, 30%, 32% (determined by GC/MS) which correspond to the deoxygenation of the ethyl oxalate side chain but also to the hydrogenolysis of the chlorine (Scheme 9).

Scheme 9: deoxygenation of **11**



On the contrary, good yield in **12** was obtained when the deoxygenation of **11** was achieved via the reduction of the hydrazone intermediate **17** (*p*-toluenesulfonyl hydrazine, cat. *p*-TsOH, EtOH, reflux) with $NaBH_3CN$ in refluxing EtOH.[23] The ethyl ester **12** of ML-3000 was obtained in 90% yield (Scheme 10).

Scheme 10: Synthesis of the ethyl ester of ML-3000



After saponification of **12** by NaOH in $EtOH/H_2O$,[6] ML-3000 was isolated (77%) and identified by comparaison with the literature spectral data.[6] The synthesis of ML-3000 is summarized in Scheme 11.

In summary, the synthesis of ML-3000 was achieved in 8 steps from 1-chloro-3-phenyl-2-propyne with an overall yield of 19% by using a thermal acid-promoted bicyclization of an ω-acetylenic amino ester and a Suzuki cross-coupling reaction between a heteroaryl triflate and (4-chlorophenyl)boronic acid as the key steps.

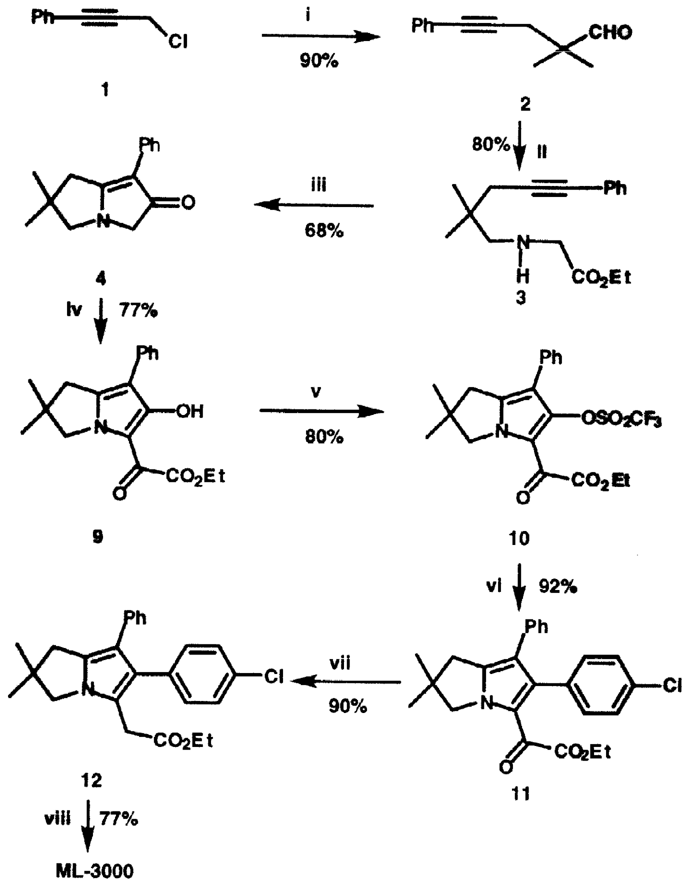
Acknowledgments: We thanks the Laboratoire L. Lafon for its financial support.

Experimental Section

General. All experiments were run under an Ar atmosphere. IR spectra were recorded in CCl_4 (NaCl cells). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 MHz and 75 MHz respectively. Chemical shifts are reported as δ values in ppm relative to internal tetramethylsilane. Mass spectra were run on a Hewlett-Packard instrument (EI mode at 70 eV). Uncorrected melting points were taken using a Kofler bank. Microanalysis, HRMS were performed at Paris VI University. Flash column chromatography was accomplished on Merck Kieselgel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254}. Solvents such as CH_2Cl_2 or 1,2-dichloroethane were distilled from CaH_2, THF was distilled from Na/benzophenone and ethanol from Mg.

2,2-Dimethyl-5-phenylpent-4-ynal (2). A mixture of 30% aqueous NaOH (5.31 g NaOH, 132.8 mmol), NaI (1 g, 6.64 mmol), n-Bu_4NI (0.49 g, 1.328 mmol) and toluene (10 mL) was heated at 50 °C. To this vigorously stirred mixture was added dropwise (ca. 1 h) a solution of 1-chloro-3-phenyl-2-propyne **1** (10 g, 66.4 mmol) and isobutyraldehyde (7.18 g, 9 mL, 99.6 mmol) in toluene (5 mL). After 24 h at 50 °C, the reaction mixture was cooled, diluted with water (100 mL) and extracted with ether (3x50 mL). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (95/5 petroleum ether/ethyl acetate) to give **2** as a colorless oil (11.13 g, 90% yield): IR 2700, 2240, 2220, 1730, 1460, 1440, 885, 690 cm^{-1}; ^1H NMR δ 1.22

Scheme 11: Synthesis of ML-3000



i - Isobutyraldehyde, cat. n-Bu_4NI, cat. NaI, NaOH/H_2O/toluene, 50 °C;
ii - Glycine methyl ester hydrochloride, $NaBH(OAc)_3$, Et_3N, CH_2Cl_2, rt;
iii - 150 °C, *t*-$BuCO_2H$ (1 equiv.);
iv - a) EtONa, $(EtOCO)_2$, EtOH, rt; b)AcOH;
v - a) NaH, THF, rt; b)$PhN(Tf)_2$, rt;
vi - (4-Chlorophenyl)boronic acid, cat. $Pd(PPh_3)_4$, Na_2CO_3/H_2O, THF, reflux;
vii - a) *p*-toluenesulfonyl hydrazine, *p*-TsOH, EtOH, reflux; b) $NaBH_3CN$, EtOH, reflux;
viii - NaOH, H_2O, EtOH, 80 °C.

(s, 6H), 2.56 (s, 2H), 7.25-7.30 (m, 3H), 7.35-7.45 (m, 2H), 9.60 (s, 1H); EI MS *m/z* (relative intensity) 186 (M^+, 4), 171 (100), 143 (44), 128 (40), 115 (93), 102 (48), 63 (20); HRMS Calcd for $C_{13}H_{14}O$: 186.1044. Found: 186.1044.

Methyl *N*-(2,2-dimethyl-5-phenylpent-4-ynyl) glycinate (3). To a solution of **2** (6 g, 32.21 mmol) in dry dichloromethane or dry 1,2-dichloroethane (100 mL) at room temperature were added powdered glycine methyl ester hydrochloride (4.25 g, 33.82 mmol) and dry triethylamine (6.52 g, 9 mL, 64.43 mmol). The resulting suspension was vigorously stirred for 15 min and powdered $NaBH(OAc)_3$ (10.24 g, 48.32 mmol) was then added by small portions. The reaction mixture was vigorously stirred for an additional 12 h, quenched by addition of saturated aqueous $NaHCO_3$ (100 mL) and, after 15 min, extracted with dichloromethane (3x100 mL). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (95/5 dichloromethane/ethyl acetate) to furnish **3** as a colorless oil (6.7 g, 80% yield): IR 2240, 2220, 1740, 1715, 1470, 1435, 1360, 1200, 1175, 690 cm^{-1}; ^1H NMR δ 1.04 (s, 6H), 1.60 (broad s, 1H), 2.38 (s, 2H), 2.53 (s, 2H), 3.44 (s, 2H), 3.71 (s, 3H), 7.25-7.30 (m, 3H), 7.35-7.45 (m, 2H); ^{13}C NMR δ 25.3 (q, 2C), 30.5 (t), 35.1 (s), 51.6 (q), 51.9 (t), 59.3 (t), 82.4 (s), 88.1 (s), 124.1 (s), 127.5 (d), 128.2 (d, 2C), 131.5 (d, 2C), 173.2 (s); EI MS *m/z* (relative intensity) 259 (M^+, 28), 200 (76), 115 (56), 102 (100), 74 (55); HRMS Calcd for $C_{16}H_{21}NO_2$: 259.1572. Found: 259.1571.

2,2-Dimethyl-7-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolizin-6-one (4). A stirred mixture of **3** (2 g, 7.71 mmol) and pivalic acid (0.787 g, 7.71 mmol) was heated at 150 °C for 5 h. Methanol was distilled during the reaction. After cooling to room temperature, the crude product was purified by flash column chromatography on silica gel (50/50 dichloromethane/ethyl acetate) to give **4** as a yellow-orange solid (1.2 g, 68% yield): IR 1665, 1600, 1465, 1365, 1310, 1170, 1130, 935, 695 cm^{-1}; ^1H NMR δ 1.25 (s, 6H), 2.85 (t, J = 2.2 Hz, 2H), 3.20 (s, 2H), 3.80 (t, J = 2.2 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H); ^{13}C NMR δ 27.9 (q, 2C), 40.1 (s), 43.9 (t), 56.7 (t), 61.3 (t), 106.5 (s), 124.5 (d), 124.9 (d, 2C), 128.3 (d, 2C), 133.1 (s), 181.0 (s), 197.2 (s); EI MS *m/z* (relative intensity) 227 (M^+, 100), 198 (54), 115 (30); HRMS Calcd for $C_{15}H_{17}NO$: 227.1310. Found: 227.1310.

6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizine (5).[6] A solution of **6** (0.25 g, 0.695 mmol) and (4-chlorophenyl)boronic acid (0.109 g, 0.695 mmol) in dry THF (7 mL) was degassed with argon for 15 min. To this solution were added $Pd(PPh_3)_4$ (0.04 g, 0.035 mmol) and 5.4 M aqueous KOH (0.45 mL, 2.43 mmol KOH). The resulting mixture was stirred at room temperature overnight and then refluxed for an additional 24 h. After cooling the solution at room temperature, the solvents were removed in *vacuo*. The residue was taken up with dichloromethane (10 mL) and filtered through a plug of Florisil, which was washed with additional dichloromethane (10 mL). The filtrate was washed with brine, dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by preparative TLC on silica gel (95/5 petroleum ether/ether) to give **5** as a grey solid (0.033 g, 15% yield): ^1H NMR δ 1.28 (s, 6H), 2.82 (s, 2H), 3.76 (s, 2H), 6.69 (s, 1H), 7.10-7.45 (m, 9H); ^{13}C NMR δ 28.0 (q, 2C), 40.2 (t), 43.5 (s), 59.8 (t), 113.3 (d), 114.4 (s), 125.0 (d), 125.5 (s), 128.1 (d, 2C), 128.2 (d, 2C), 128.6 (d, 2C), 129.5 (d, 2C), 131.0 (s), 135.1 (s), 135.8 (s), 136.1 (s); EI MS *m/z* (relative intensity) 323 (38), 321 (M^+, 100), 265 (45), 230 (40), 202 (33), 125 (23).

2,2-Dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-6-yl trifluoromethanesulfonate (6). To a stirred suspension of NaH (60% in mineral oil) (0.193 g, i.e. 0.116 g NaH, 4.84 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of **4** (1 g, 4.40 mmol) in dry THF (10 mL). The resulting red solution was stirred at room temperature for 1 h and then cooled to 0 °C. *N*-Phenyltrifluoromethanesulfonimide (1.886 g, 5.28 mmol) was then added in one portion. After 5 min at 0 °C and then 20 h at room temperature, the resulting solution was dilute with brine (25 mL) and extracted with ethyl acetate (3x20 mL). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (80/20 petroleum ether/dichloromethane) to furnish **6** as a white solid (1.14 g, 72% yield): mp 56-58 °C; IR 1610, 1430, 1410, 1380, 1210, 1145, 930, 700 cm^{-1}; ^1H NMR δ 1.27 (s, 6H), 2.83 (s, 2H), 3.72 (s, 2H), 6.71 (s, 1H), 7.17-7.45 (m, 5H); ^{13}C NMR δ 27.7 (q, 2C), 41.2 (t), 42.6 (s), 60.6 (t), 106.1 (d), 109.1 (s), 118.7 (q, J = 321 Hz, OSO_2CF_3), 125.9 (d), 127.0 (d, 2C), 128.6 (d, 2C), 131.7 (s), 132.7 (s), 133.9 (s); EI MS *m/z* (relative intensity) 359 (M^+, 26), 226 (100), 115 (27); Anal. Calcd for $C_{16}H_{16}F_3NO_3S$: C, 53.47; H, 4.49; N, 3.90. Found: C, 53.47; H, 4.44; N, 3.76.

***N,N*-Diethyl 2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-6-yl carbamate (7).** Prepared from **4** (1 g, 4.40 mmol) by the same procedure used for the preparation of **6**, employing diethylcarbamyl chloride (0.716 g, 5.28 mmol) instead of $PhNTf_2$. Purification by flash column chromatography on silica gel (95/5 dichloromethane/ethyl acetate) gave **7** as a slightly yellow solid (1.02 g, 71% yield): mp 68-70 °C; IR 1720, 1610, 1475, 1425, 1385, 1270, 1240, 1170, 1150, 700 cm^{-1}; ^1H NMR δ 1.10-1.25 (m, 6H), 1.25 (s, 6H), 2.83 (s, 2H), 3.30-3.50 (m, 4H), 3.69 (s, 2H), 6.71 (s, 1H), 7.08-7.45 (m, 5H); ^{13}C NMR δ 13.4 (q), 14.2 (q), 27.9 (q, 2C), 41.4 (t), 41.7 (t), 42.1 (t), 42.4 (s), 60.3 (t), 105.1 (d), 108.2 (s), 124.7 (d), 126.9 (d, 2C), 128.2 (d, 2C), 130.8 (s), 135.0 (s), 136.9 (s), 154.2 (s); EI MS *m/z* (relative intensity) 326 (M^+, 40), 226 (30), 115 (33), 100 (100), 72 (31); HRMS Calcd for $C_{20}H_{26}N_2O_2$: 326.1994. Found: 326.1988.

Diethyl 2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-6-yl phosphate (8). Prepared from **4** (1 g, 4.40 mmol) by the same procedure used for the preparation of **6**, employing diethyl chlorophosphate (0.911 g, 5.28 mmol) instead of $PhNTf_2$. Purification by flash column chromatography on silica gel (50/50 petroleum ether/ethyl acetate) gave **8** as a red solid (0.99 g, 62% yield): mp 58-60 °C; IR 1610, 1395, 1275, 1040, 965, 700 cm^{-1}; ^1H NMR δ 1.25 (s, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.82 (s, 2H), 3.67 (s, 2H), 4.02-4.20 (m, 4H), 6.66 (s, 1H), 7.10-7.55 (m,5H); ^{13}C NMR δ 16.0 (q), 16.1 (q), 27.8 (q, 2C), 41.6 (t), 42.4 (s), 60.3 (t), 64.3 (t), 64.4 (t), 103.6 (d), 107.6 (s), 124.9 (d), 126.8 (d, 2C), 128.3 (d, 2C), 131.1 (s), 134.5 (s), 136.1 (s); EI MS *m/z* (relative intensity) 363 (M^+, 100), 227 (50), 171 (72), 115 (79); HRMS Calcd for $C_{19}H_{26}NO_4P$: 363.1599. Found: 363.1596.

Ethyl 2-(2,2-dimethyl-6-hydroxy-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)-2-oxoacetate (9). Small pieces of sodium metal (0.394 g, 17.16 mmol) were carefully added to dry ethanol (10 mL) stirred at 0 °C. After disappearance of the sodium, a solution of **4** (1.3 g, 5.72 mmol) and diethyl oxalate (0.919 g, 0.854 mL, 6.29 mmol) in dry ethanol (10 mL) was added dropwise. The resulting solution was stirred at room temperature for 15 h. The reaction was stopped by addition of acetic acid (2.5 mL), followed by addition of water (2.5 mL). Solvents were removed in *vacuo* and the residue was taken up with water

(50 mL) and extracted with ethyl acetate (50 mL, then 2x25 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (80/20 petroleum ether/ethyl acetate) to give **9** as a yellow-green solid (1.436 g, 77% yield): mp 123-125 °C; IR 3100(broad), 1730, 1690, 1600, 1570(broad), 1270, 1040, 695 cm^{-1}; ^1H NMR δ 1.27 (s, 6H), 1.46 (t, J = 7.2 Hz, 3H), 2.87 (s, 2H), 4.13 (s, 2H), 4.48 (q, J = 7.2 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 11.33 (s, 1H); ^{13}C NMR δ 13.9 (q), 27.9 (q, 2C), 41.2 (s), 41.9 (t), 62.6 (t), 63.8 (t), 106.2 (s), 116.7 (s), 125.7 (d), 126.8 (d, 2C), 128.4 (d, 2C), 133.0 (s), 148.5 (s), 154.7 (s), 165.8 (s), 166.7 (s); EI MS *m/z* (relative intensity) 327 (M^+, 43), 254 (100), 115 (14); HRMS Calcd for $C_{19}H_{21}NO_4$: 327.1470. Found: 327.1454.

Ethyl 2-(2,2-dimethyl-7-phenyl-6-trifluoromethanesulfonyloxy-2,3-dihydro-1*H*-pyrrolizin-5-yl)-2-oxoacetate (10). To a stirred suspension of NaH (60% in mineral oil) (0.183 g, i.e. 0.109 g NaH, 4.582 mmol) in dry THF (10 mL) at room temperature was added dropwise a solution of **9** (1 g, 3.054 mmol) in dry THF (10 mL) . The resulting orange suspension was stirred at room temperature for 1 h. *N*-Phenyltrifluoromethanesulfonimide (1.31 g, 3.665 mmol) was then added in one portion. After 12 h at room temperature, the resulting solution was dilute with brine (20 mL) and water (20 mL), and extracted with ethyl acetate (50 mL, then 2x25 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (85/15 petroleum ether/ethyl acetate) to furnish **10** as a colorless oil (1.12 g, 80% yield): IR 1740, 1650, 1460, 1430, 1385, 1210, 1140, 1035, 940, 695 cm^{-1}; ^1H NMR δ 1.29 (s, 6H), 1.42 (t, J = 7.2 Hz, 3H), 2.87 (s, 2H), 4.16 (s, 2H), 4.42 (q, J = 7.2 Hz, 2H), 7.25-7.45 (m, 5H); ^{13}C NMR δ 13.8 (q), 27.8 (q, 2C), 40.9 (t), 41.7 (s), 62.9 (t), 63.0 (t), 113.1 (s), 117.5 (s), 118.3 (q, J = 320 Hz, OSO_2CF_3), 127.5 (d), 128.1 (d, 2C), 128.8 (d, 2C), 130.4 (s), 136.9 (s), 142.1 (s), 162.6 (s), 173.4 (s); EI MS *m/z* (relative intensity) 327 (M^+ + H - SO_2CF_3, 40), 254 (100), 115 (20).

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)-2-oxoacetate (11). A solution of **10** (0.6 g, 1.3 mmol) and (4-chlorophenyl)boronic acid (0.224 g, 1.43 mmol) in dry THF (10 mL) was degased with argon for 15 min. To this solution were added $Pd(PPh_3)_4$ (0.075 g, 0.065 mmol) and Na_2CO_3 (0.35 g) solubilized in a minimum water (1 mL). The resulting mixture was vigorously stirred at room temperature for 1 h and then refluxed for an additional 1 h. After cooling to room temperature, the suspension was diluted with ether (25 mL) and filtered through a plug of Celite, which was washed by additional ether (20 mL). The filtrate was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (90/10 petroleum ether/ethyl acetate) to give **11** as a slightly yellow solid (0.51 g, 92% yield): mp 84-86 °C; IR 1740, 1625, 1600, 1425, 1380, 1185, 1065, 700 cm^{-1}; ^1H NMR δ 1.05 (t, J = 7.2 Hz, 3H), 1.32 (s, 6H), 2.85 (s, 2H), 3.60 (q, J = 7.2 Hz, 2H), 4.23 (s, 2H), 6.95-7.40 (m, 9H); ^{13}C NMR δ 13.5 (q), 28.0 (q, 2C), 40.2 (t), 42.9 (s), 61.8 (t), 62.1 (t), 119.4 (s), 121.8 (s), 126.2 (d), 128.1 (d, 2C), 128.3 (d, 2C), 128.5 (d, 2C), 132.2 (d, 2C), 132.3 (s), 133.4 (s), 133.8 (s), 136.0 (s), 145.6 (s), 164.8 (s), 176.5 (s); EI MS *m/z* (relative intensity) 423 (7), 421 (M^+, 20), 350 (35), 348 (100); HRMS Calcd for $C_{25}H_{24}ClNO_3$: 421.1444. Found: 421.1445.

Ethyl 2-(6-(4-chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)acetate (12).[6] A stirred suspension of **11** (0.97 g, 2.3 mmol), *p*-toluenesulfonhydrazide (0.471 g, 2.53 mmol) and *p*-TsOH.H_2O (0.115 g) in dry ethanol (9 mL) was refluxed for 7 h. After cooling to room temperature, a solution of $NaBH_3CN$ (0.578 g, 9.2 mmol) in dry ethanol (6 mL) was added dropwise to the yellow suspension, which was then refluxed for an additional 4 h. The resulting solution was cooled to room temperature and ethanol was removed in *vacuo*. The residue was taken up with water (30 mL) and extracted with ethyl acetate (3x20 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel (95/5 petroleum ether/ethyl acetate) to give **12** as a slightly yellowish solid (0.84 g, 90% yield): mp 87-89 °C; IR 1735, 1600, 1485, 1450, 1370, 1175, 1100, 1030, 700 cm^{-1}; ^1H NMR δ 1.28 (t, J = 7.2 Hz, 3H), 1.30 (s, 6H), 2.85 (s, 2H), 3.51 (s, 2H), 3.75 (s, 2H), 4.18 (q, J = 7.2 Hz, 2H), 7.00-7.27 (m, 9H); ^{13}C NMR δ 14.2 (q), 28.0 (q, 2C), 31.6 (t), 40.6 (t), 43.3 (s), 58.4 (t), 61.0 (t), 114.8 (s), 117.7 (s), 123.6 (s), 124.7 (d), 128.0 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 131.6 (s), 131.7 (d, 2C), 134.1 (s), 134.7 (s), 136.0 (s), 170.8 (s); EI MS *m/z* (relative intensity) 409 (12), 407 (M^+, 36), 336 (33), 334 (100), 299 (14), 242 (14); HRMS Calcd for $C_{25}H_{26}ClNO_2$: 407.1652. Found: 407.1653.

Diethyl 2,2-dimethyl-6-oxo-7-phenyl-2,3,5,6-tetrahydro-1*H*-pyrrolizine-5,5-diacetate (14). To a stirred solution of LDA (1.3 mmol) in dry THF (3 mL) at 0 °C was added dropwise a solution of **4** (0.227 g, 1 mmol) in dry THF (2 mL). The resulting red solution was stirred at 0 °C for 15 min. Ethyl bromoacetate (0.25 g, 1.5 mmol) was then added in one portion and the resulting solution was stirred at 0 °C for 5 h. The reaction mixture was diluted with water (10 mL) and extracted with ether (3x10 mL). The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the residue was purified by preparative TLC on silica gel (80/20 dichloromethane/ethyl acetate) to furnish **14** as an oil (0.25 g, 63% yield): IR 1740, 1670, 1605, 1375, 1185, 1035, 700 cm^{-1}; ^1H NMR δ 1.15 (t, J = 7.5 Hz, 6H), 1.26(s, 6H), 2.78 (d, J = 16 Hz, 2H), 2.87 (d, J = 16 Hz, 2H), 2.90 (s, 2H), 3.42 (s, 2H), 4.05 (q, J = 7.5 Hz, 4H), 7.09 (t, J = 7.3 Hz, 1H), 7.30 (t, J = 7.3 Hz, 2H), 7.63 (d, J = 7.3 Hz, 2H); ^{13}C NMR δ 14.1 (q, 2C), 27.8 (q, 2C), 39.1 (t, 2C), 39.7 (s), 43.9 (t), 58.8 (t), 60.8 (t, 2C), 65.5 (s), 104.4 (s), 124.6 (d), 125.1 (d, 2C), 128.3 (d, 2C), 133.1 (s), 169.3 (s, 2C), 179.3 (s), 198.2 (s); EI MS *m/z* (relative intensity) 399 (M^+, 100), 312 (22), 224 (20); HRMS Calcd for $C_{23}H_{29}NO_5$: 399.2046. Found: 399.2046.

2-(6-(4-Chlorophenyl)-2,2-dimethyl-7-phenyl-2,3-dihydro-1*H*-pyrrolizin-5-yl)acetic acid (ML-3000).[6] To a stirred solution of **12** (0.408 g, 1 mmol) in absolute ethanol (3 mL), heated at 80 °C, was added a solution of 10% aqueous NaOH (0.55 mL). After an additional 15 min at 80 °C, the solution was cooled to 0 °C, diluted with water (5 mL) and acidified to pH 6-7 with a 1 M aqueous phosphoric acid solution. The mixture was extracted with ether/dichloromethane (3/1, 3x20 mL), the organic phase was dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* and the solid residue was washed with isopropyl ether, filtered off and dried in *vacuo* to give **ML-3000** as a slightly yellowish solid (0.292 g, 77% yield): mp 162-163 °C; IR 3520(broad), 1710(broad), 1600, 1485, 1090, 910, 700 cm^{-1}; ^1H NMR δ 1.30 (s, 6H), 2.86 (s, 2H), 3.59 (s, 2H), 3.76 (s, 2H), 7.00-7.30 (m, 9H), 9.30 (s, CO_2H); ^{13}C NMR δ 28.0 (q, 2C), 31.1 (t), 40.5 (t), 43.3 (s), 58.4 (t), 114.9 (s), 116.8 (s), 124.0 (s), 124.7 (d), 128.0 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 131.6 (d, 2C), 131.8 (s), 134.4 (s), 134.5 (s), 135.8 (s), 176.1 (s); EI MS $C_{23}H_{22}ClNO_2$ *m/z* (relative intensity) 337(35), 335(M^+ - CO_2 , 100), 278 (12), 264 (15), 244 (14), 202(27).

References and Notes

(1) Lombardino, J.G. *Nonsteroidal Antiinflammatory Drugs* ; Wiley Interscience, John Wiley & Sons: New York, **1983**.

(2) Amadio, P.; Cummings, D.M.; Amadio, P. *Postgrad. Med.* **1993,** *93*, 73-97.

(3) Cryer, B.; Feldmann, M. *Arch. Intern. Med.* **1992**, *152* , 1145-1155.

(4) Asako, H.; Kubes, P.; Wallace, J.; Gaginella, T.; Wolf, R.E.; Granger, N. *Am. J. Physiol.* **1992,** *262*, G 903-G 908.

(5) Kuehl, F.A.; Daugherty, H.W.; Ham, E.A. *Biochem. Pharmacol.* **1984**, *33*, 1-5.

(6) Laufer, S.A.; Augustin, J.; Dannhardt, G.; Kiefer, W. *J. Med. Chem.* **1994,** *37*, 1894-1897.

(7) Rabasseda, X.; Mealy, N.; Castaner, J. *Drugs Future* **1995**, 20, 1007-1009.

(8) Laufer, S.; Striegel, H.-G.; Neher, K.; Zechmeister, P.; Donat, C.; Stolingwa, K.; Baur, S.; Tries, S.; Kammermeier, T.; Dannhardt, G.; Kiefer, W. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 307-312.

(9) Cossy, J.; Belotti, D.; Bellosta, V.; Boggio, C. *Tetrahedron Lett.* **1997**, *38*, 2677-2680.

(10) a - Belotti, D.; Cossy, J. *Synlett* **1997**, 1249-1250. b - Cossy, J.; Belotti, D. *J. Org. Chem.* **1997**, *52*, 7900-7901. c - Cossy, J; Belotti, D. French Patent 9612760, Oct. 21, **1996**; PCT/EP 97/05812, WO 98 17666, June 11, **1998.**

(11) a - Zwierzak, A.; Tomassy, *Synth. Commun.* **1996**, *26*, 3593-3600. b - Lee, J.B.; Downie, I.M. *Tetrahedron* **1967**, 359-363.

(12) Dietl, H.K.; Brannock, K.C. *Tetrahedron Lett.* **1973,** 1273-1275.

(13) Abdel-Magid, A.F.; Carson, K.G.; Harris, B.D.; Maryanoff, C.A.; Shah, R.D. *J. Org. Chem.* **1996,** *61*, 3849-3862.

(14) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985,** *26,* 4763-4766.

(15) Miyaura N.; Suzuki, A. *Chem. Rev.* **1995,** 95, 2457-2483.

(16) Stille, J.K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25,* 508-524.

(17) Sengupta, S.; Leite, M.; Raslan, D.S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992,** *57*, 4066-4068.

(18) Armstrong, R.J.; Harris, F.L. Weiler, L. *Can. J. Chem.* **1982**, *60,* 673-675.

(19) Ritter, K. *Synthesis* **1993**, 735-762.

(20) Kirschning, A.; Ries, M.; Domann, S.; Martin, W.; Albrecht, W.; Arnold, P.; Laufer, S. *Bioorg. & Med. Chem. Lett.* **1997**, *7*, 903-906.

(21) Snyder, H.R.; Brooks, L.A.; Shapiro, S.H. *Organics Syntheses* ; Wiley: New York, **1943** ; Collect. Vol. II, pp 531-534.

(22) Ram, S.; Spicer, L.D. *Tetrahedron Lett.* **1988,** *29,* 3741-3744.

(23) Hutchins, R.O.; Milewski, C.A.; Maryanoff, B.E. *J. Am. Chem. Soc.* **1973,** *95*, 3662-3668.