Communications

Synthesis of ML-3000, an Inhibitor of Cyclooxygenase and 5-Lipoxygenase

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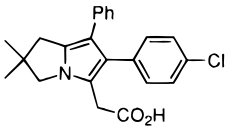
Dual inhibitors of cyclooxygenase and 5-lipoxygenase of the arachidonic acid cascade have potential as agents for the treatment of arthritis.[1,2] Recently, 2,3-dihydro-1*H*-pyrrolizine derivatives such as ML-3000 have been proven to selectively inhibit the enzymes cyclooxygenase (IC_{50} = 0.2l μM) and 5-lipoxygenase (IC_{50} = 0.18 μM).[1,2] ML-3000 is the most potent and well-balanced dual inhibitor of both enzymes. However, the previous synthesis of this nonsteroidal antiinflammatory drug proceeds with poor overall yield (<5%).[1]

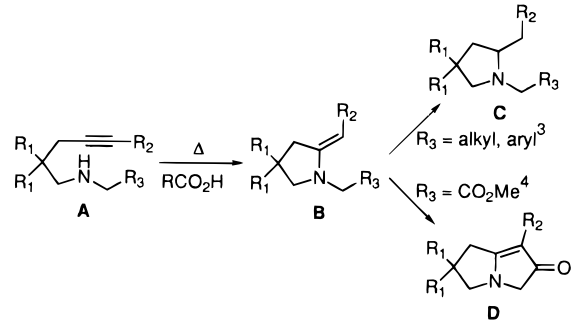


ML-3000

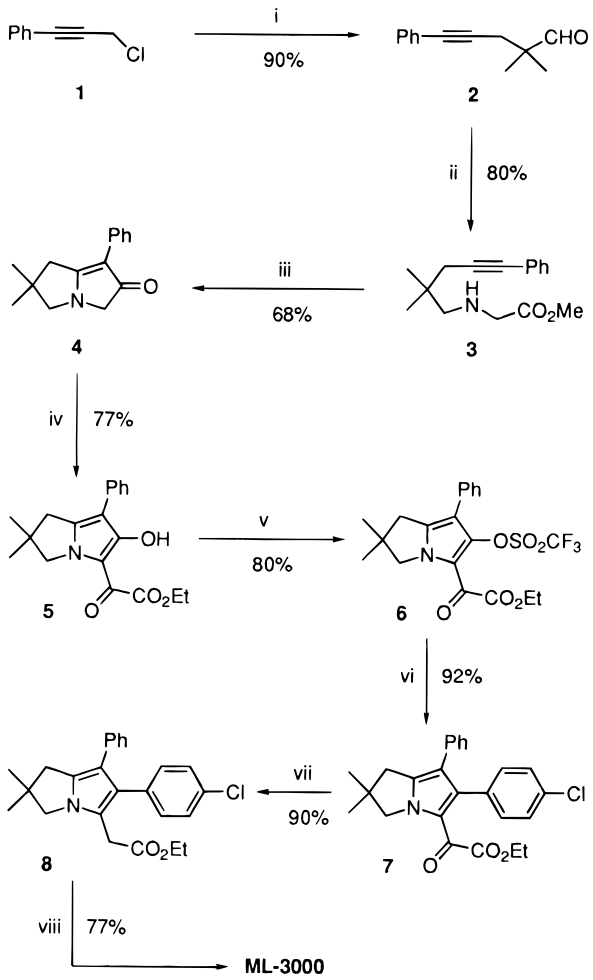
Herein, we report a short and efficient synthesis of ML-3000 that features a thermal acid-promoted bicyclization of an ω-acetylenic amino ester. In a previous paper, we described a convenient synthetic method that provided access to polysubstituted pyrrolidines based on thermal cyclization of ω-acetylenic amines.[3] A smooth thermolysis of ω-acetylenic amines **A** in the presence of 1 equiv of acetic acid or pivalic acid without solvent led to cyclic enamines **B**, which could be reduced to the corresponding pyrrolidines **C**. Furthermore, we have reported an extension of this method in which the enamine **B** is trapped intramolecularly with an appropriate acceptor such as an ester group to provide an efficient synthesis of substituted 2,3,5,6-tetrahydro-6-oxo-1*H*-pyrrolizines **D**.[4,5] (Scheme 1).

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. Treatment of chloride **1** with isobutyraldehyde under basic phase-transfer catalysis[6] in the presence of a catalytic amount of NaI produced the aldehyde **2** (90%). This aldehyde was condensed with methyl glycinate hydrochloride under reductive amination conditions[7] to furnish the ω-acetylenic amino ester **3** (80%). In the key step, the tetrahydro-6-oxo-1*H*-pyrrolizine **4** was isolated in good yield (68%) when the

Scheme 1



Scheme 2. Synthesis of ML-3000[a]



[a] Key: (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 or 1,2-dichloroethane, rt; (iii) Δ, 150 °C, 1 equiv of *t*-$BuCO_2H$; (iv) (a) EtONa, $(EtOCO)_2$, EtOH, rt, (b) AcOH; (v) (a) NaH, THF, rt, (b) $PhN(SO_2CF_3)_2$, rt; (vi) (4-chlorophenyl)-boronic acid, cat. $Pd(PPh_3)_4$, Na_2CO_3/H_2O, THF, reflux; (vii) (a) *p*-toluenesulfonyl hydrazide, cat. *p*-TsOH, EtOH, reflux, (b) $NaBH_3CN$, EtOH, reflux; (viii) NaOH, H_2O, EtOH, 80 °C.

ω-acetylenic amino ester **3** was heated at 150 °C in the presence of 1 equiv of pivalic acid without solvent.[4,5] The carboxylic acid side chain of ML-3000 was introduced by acylation of the tetrahydro-6-oxo-1*H*-pyrrolizine with diethyl oxalate under basic conditions.[8] The resulting β-diketone **5** (77%) was entirely enolized. The introduc-

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tion of the *p*-chlorophenyl group was achieved by using a Suzuki cross-coupling reaction.[9] After treatment of the sodium enolate of **5** with *N*-phenyltrifluoromethanesulfonimide,[10] the resulting triflate **6** (80%) was coupled with (4-chlorophenyl)boronic acid in the presence of a catalytic amount of $Pd(PPh_3)_4$ and Na_2CO_3/H_2O in refluxing THF to produce compound **7** (92%). Deoxygenation of compound **7** via the *p*-toluenesulfonylhydrazone[11] furnished the ethyl ester of ML-3000 (**8**, 90%), which after saponification[1] led to ML-3000 (77%). The structure of ML-3000 was confirmed by a comparison of its spectral data with those reported in the literature[1] (Scheme 2).

In summary, ML-3000 was synthesized in eight steps from 1-chloro-3-phenyl-2-propyne with an overall yield of 19%. The sequence features the use of a thermally induced bicyclization of an ω-acetylenic amino ester.

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Supporting Information Available: Full experimental procedures and spectroscopic data are available for compounds **2**−**8** and **ML-3000** (5 pages).

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