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Synthesis of the Angiotensin Converting Enzyme Inhibitor (−)-A58365A via an Isomünchnone Cycloaddition Reaction

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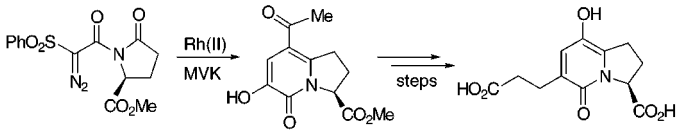
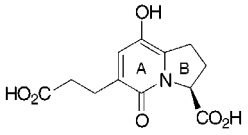
ABSTRACT

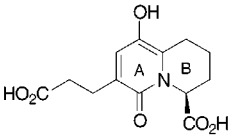


The angiotensin converting enzyme inhibitor (−)-A58365A (1) was synthesized by a process based on the [3 + 2]-cycloaddition reaction of a phenylsulfonyl-substituted isomünchnone intermediate. The starting material for this process was prepared from L-pyroglutamic acid and involved using a diazo-phenylsulfonyl-substituted pyrrolidine imide. Treatment of the diazoimide with $Rh_2(OAc)_4$ in the presence of methyl vinyl ketone afforded a 3-hydroxy-2-pyridone derivative which was subsequently converted to the ACE inhibitor in six additional steps.

The 2(1*H*)-pyridone ring system is a valuable building block in natural product synthesis,[1] as it can act as a common intermediate for the preparation of a wide variety of piperidine, pyridine, quinolizidine, and indolizidine alkaloids.[2,3] *N*-Alkyl-substituted pyridones have been found to exhibit a wide range of biological activities.[4] These include anticancer/antitumor activity[5] as well as cardiovascular[6] and antiinfective behavior as with HIV-reverse transcriptase inhibitors.[7] The pyridone substructure is also found in a large number of natural products such as camptothecin,[8] elastase,[9] and thrombin.[10] Recently, the 4-hydroxypyridone acids **1** and **2** were obtained from the fermentation broth of a soil bacterium in the Eli Lilly laboratories and were discovered to be ACE inhibitors at nanomolar concentrations.[11]



1; A58365A



2; A58365B

Substituted 2-pyridones are generally prepared from acyclic starting materials which often incorporate a Michael

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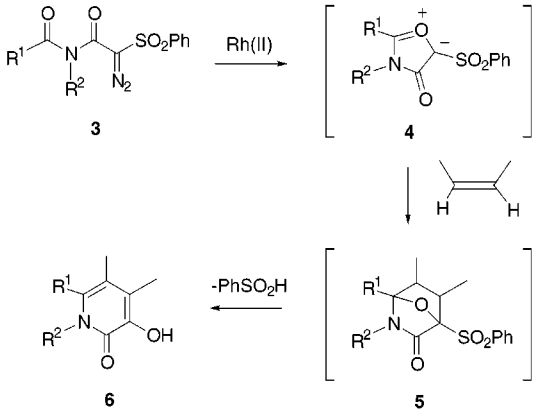
addition as the key synthetic step.[12,13] However, only a few methods of preparing hydroxy-2(1*H*)-pyridones have been reported,[14] and they typically involve harsh conditions that preclude the presence of sensitive functional groups.[15] We have recently described a general and flexible entry to a variety of 3-hydroxy-substituted pyridones.[16] The cornerstone of our synthetic plan is the [3 + 2]-cycloaddition of a phenylsulfonyl-substituted isomünchnone intermediate (i.e., **4**).[17,18] Once the cycloaddition reaction occurs, the resulting adduct **5** undergoes ready ring opening to give the desired pyridone **6** (Scheme 1).[19] The versatility of the strategy lies

Scheme 1

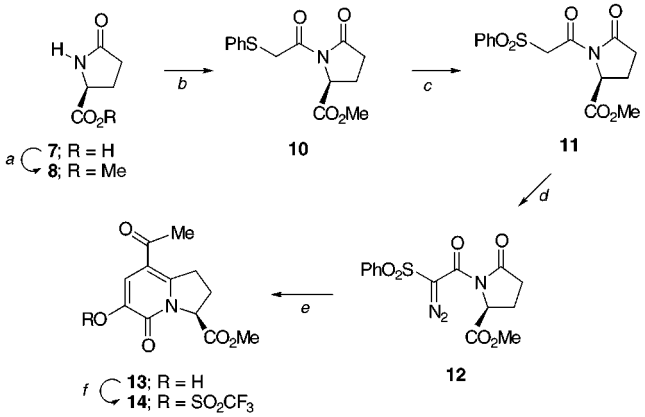


in the fact that by appropriate selection of the diazo precursor **3** and dipolarophile, various groups can be introduced into the N-1, C-4, C-5, and C-6 positions. Moreover, substituents can be incorporated into the C-3 position by conversion of the hydroxyl functionality to a triflate group,[20] followed by a palladium-catalyzed cross-coupling reaction.[21] To highlight the method, the above synthetic strategy was applied to the angiotensin converting enzyme inhibitor (−)-A58365A (**1**).

The first total synthesis of A58365A (**1**) was reported by Danishefsky and Fang in 1989[22] and more recently by the Moeller[23] and Clive groups.[24] Each of the synthetic routes utilized involved a fundamentally different strategy. Annulation of a vinylogous urethane with α-methylene glutaric anhydride was the key reaction employed in Danishefsky's synthesis.[22] In the Moeller approach, an aniodic amide oxidation−iminium ion cyclization sequence was employed for the construction of the bicyclic lactam peptide mimetic.[23] Finally, Clive's method was based on an ene−yne cyclization involving the addition of tributylstannyl radical to a terminal alkyne followed by a subsequent 6-*endo*-*trig* cyclization onto a cyclic enamide.[24] Our interest in establishing phenylsulfonyl-substituted isomünchnones as useful building blocks for 2-pyridones prompted us to apply the method outlined in Scheme 1 toward the synthesis of A58365A.

The four-step conversion of commercially available L-pyroglutamic acid (**7**) to the isomünchnone precursor **12** was carried out using conventional chemistry. Esterification of **7** with methanol in the presence of Dowex ion-exchange resin gave methyl ester **8** in 98% yield. Treatment of **8** with (phenylthio)acetyl chloride (**9**) in benzene afforded methyl 5-oxo-1-(2-phenylthioacetyl)pyrrolidine-2-carboxylate (**10**) in 87% yield. Oxidation of **10** with Oxone furnished sulfone **11** (67%) which was converted to diazoimide **12** using established diazotization procedures[25] in 91% yield. Reaction of **12** with methyl vinyl ketone and a catalytic quantity of $Rh_2(OAc)_4$ in benzene at 80 °C provided the expected 3-hydroxy-2(1*H*)-pyridone **13** in 86% isolated yield (Scheme 2). Cycloadduct **13** was easily converted to the corresponding triflate **14** (94%) by treatment with *N*-phenyltrifluoromethanesulfonamide and triethylamine.[26] The synthetic potential of

Scheme 2



Reagents: (a) MeOH, Dowex ; (b) $PhSCH_2COCl$ (**9**), benzene, 80 °C; (c) Oxone, MeOH, 25 °C; (d) p-$CH_3CONHC_6H_4SO_2N_3$, NEt_3; (e) $Rh_2(OAc)_4$, CH_2=$CHCOCH_3$, benzene, 80 °C; (f) $(TfO)_2NPh$, NEt_3, 25 °C

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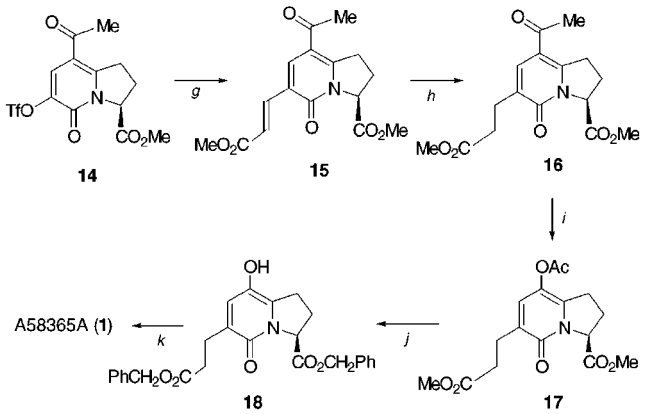
vinyl triflates has been well-established over the past decade,[20] and these compounds have been shown to be suitable substrates in various types of coupling reactions, including Heck reactions.[27] Thus, the reaction of **14** with methyl acrylate in the presence of $Pd(PPh_3)Cl_2$ at 25 °C in acetonitrile gave the prop-2-enoate derivative **15** in 86% yield (Scheme 3). Catalytic hydrogenation of **15** proceeded in quantitative yield to afford pyridone **16**. The next step involved the trifluoroperacetic acid induced Baeyer−Villiger oxidation of **16** to give acetate **17** in 96% yield. Compound **17** underwent transesterification and acetate cleavage to produce the dibenzyl ester **18** (98%, $[\alpha]^{25}_D$ −146° (CH_2Cl_2, *c* 0.39) when subjected to heating with Otera's catalyst in the presence of benzyl alcohol/toluene.[28] Catalytic hydrogenation (Pd/C) of **18** in methanol has already been reported to afford A58365A (**1**) in 96% yield.[22]

Scheme 3



Reagents: (g) CH_2=$CHCO_2Me$, $Pd(PPh_3)_2Cl_2$, NEt_3; (h) H_2, Pd/C, $CHCl_3$; (i) H_2O_2, CF_3CO_2H, 25 °C; (j) $PhCH_2OH$, toluene, Otera's catalyst, 120 °C; (k) H_2, Pd/C, MeOH.

In summary, a formal synthesis of A58365A (**1**) in 11 steps in 32.6% overall yield starting from L-pyroglutamic acid has been achieved. This synthesis underscores the flexibility provided by the [3 + 2]-cycloaddition reaction of phenylsulfonyl isomünchnones. Further utilization of the tandem cyclization−cycloaddition sequence for the stereocontrolled synthesis of other 2-pyridone natural products is under current investigation.

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