Introduction

α-Cyclopiazonic acid (CPA)

α-Cyclopiazonic acid (CPA) is a metabolite produced by Penicillium and Aspergillus fungi. Its first isolation was reported by Holzapfel in 1968.[1] CPA inhibits the sarco(endo)plasmic reticulum Ca2+−ATPase (SERCA). As shown by x-ray crystal structure analyses Thapsigargin as well as the structurally related Artemisinin, a novel drug against malaria, bind to SERCA, too.[2] Recently CPA has been found to inhibit both chloroquine sensitive (3D7) and resistant (K1) strains of Plasmodium falciparum in the low micromolar range (1.5 - 3.0 μM).

Structurally Simplified CPA Analogues

Based on preceding structure activity investigations the tetracarboxylic moiety was found to be an essential part of the pharmacophoric unit. Additionally molecular modeling studies suggest that the complete ring architecture of CPA might not be necessary for SERCA inhibition. To prove this hypothesis the structurally simplified tricyclic CPA analogues 15 and 16 were designed and synthesized.

Reagents and Conditions: (a) TFAA, pyr, DCM, rt, over night, 87%; (b) IPy, DCM, 0 ºC → rt, over night, 92%; (c) NaOH (aq), EtOH, reflux, over night, 89%; (d) SOCl2, HCl, Et2O, reflux, 89%; (e) NaOH (aq), THF/toluene 1:1, 80 ºC, 6 h, 63%; (f) SOCl2, NaH, THF, reflux, 89%; (g) NaHMDS, trisyl azide, THF, -78 ºC, 72%; (h) NaOH (aq), THF/toluene 1:1, 20:1, 80 ºC, 16 h, 67%.

Synthesis of Intermediate 6 via Route B

Intermediate 25 was prepared in six steps from (R)-Carvone following literature procedures.[3] Attempts to convert 23b directly to 24 by an organocatalytic alkylation of imine 28 failed, probably due to sterically hindrance of the isopropenyl group. As an alternative we prepared bromides 25a and 25b in high diastereoselectivitites. Bromide 25b was then used as an electrophile for the alkylation of 29. Depending on the reaction conditions phenol 26 or the Michael addition product 29 were isolated. The 1,4-addition can be avoided by protecting the carbonyl group as a ketal.

Reagents and Conditions: (a) TFAA, pyr, DCM, rt, over night, 87%; (b) IPy, BF3, HBF4, DCM/TFA 10:1, rt, over night, 55%; (c) TICl, CHCl3, rt, 6 h, 63%; (d) NaH (aq). EDC, reflux, over night, 89%; (f) SOCl2, MeOH, 0 ºC → rt, over night, 69%; (g) 1. 18, toluene, 110 ºC, 30 min. 2. KOH, 110 ºC, 30 min, 67%.

Summary

- A route to simplified tricyclic CPA analogues including the tetracarboxylic acid moiety was found to be an essential part of the pharmacophoric unit. The protected optically active key intermediate 1 can be obtained following the Knight procedure with a modified reduction step. The direct enantioselective catalytic azidination of 4 and subsequent reaction with acetic acid yielded the ring-opened product 31 in an one-pot-reaction.

- The diastereoselective Michael addition of Grignard reagent 22 to 2 afforded 19 in good to excellent diastereomeric ratios. The protected optically active key intermediate 1 can be obtained following the Knight procedure with a modified reduction step. The direct enantioselective catalytic azidination of 4 and subsequent reaction with acetic acid yielded the ring-opened product 31 in an one-pot-reaction.

- The optically active key intermediate 20 (route A) was prepared by diastereoselective Michael addition using Evans chiral auxiliaries. 31 was obtained by a direct catalytic azidination.

- Carvone derivative 25a (route B) was synthesized by a highly regio- and diastereoselective bromination of 23a with ammonium tribromide.

References: