2nd World Congress of the Board of Pharmaceutical Sciences of FIP

The Global Translation of Science into Drug Development in Advancing Therapy

May 30 - June 3, 2004

Kyoto International Conference Hall, Japan

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2nd FIP PHARMACEUTICAL SCIENCES WORLD CONGRESS

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P3E-V-012 Investigation of stereoselective asymmetric Pummerer reaction and Pummerer-type cyclization

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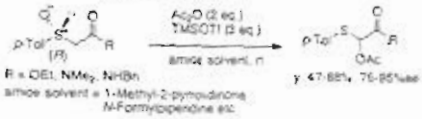
Purpose: Pummerer reactions, providing various α-substituted sulfides from the corresponding sulfoxides, have been attractive in regard to their value in the synthesis of natural products and biologically active compounds. We wished to develop highly enantioselective Pummerer reactions based on the concept of nonbonded S···O interaction and investigate application to Pummerer-type cyclizations.

Methods and Results: Chiral *p*-tolyl sulfinylacetic acid derivatives were treated with Ac_2O (2.0 mol eq.), trimethylsilyl triflate (TMSOTf) (3.0 mol eq.) in an amide solvent at room temperature to give the corresponding α-acetoxy sulfides in 76-95% ee. We also attempted at application of asymmetric Pummerer-type cyclization in an amide solvent.



Conclusion: We demonstrated a novel simple procedure for highly stereoselective Pummerer reactions based on the concept of nonbonded S··· interactions.

P3E-V-013 Synthesis of the pendant moiety of oral 1β-methylcarbapenem antibiotic L-084 using 1-azabicyclo[1.1.0]butane

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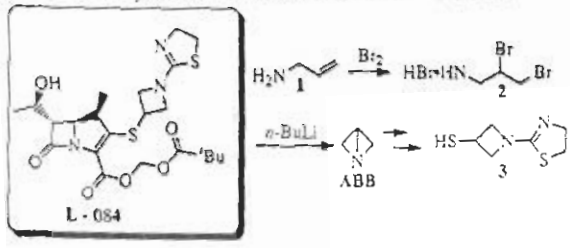
Purpose: **L-084** is a new oral 1β-methylcarbapenem antibiotic with a broad spectrum and a potent antibacterial activity against various clinically isolated bacteria. We wished to develop an efficient synthetic method for the pendant (**3**) of **L-084** *via* 1-azabicyclo[1.1.0]butane (**ABB**; useful for the synthesis of azetidine derivatives.

Methods & Results: Remarkably strained **ABB** was synthesised in a high yield by cyclization of 2,3-dibromopropylamine hydrobromide (**2**), obtained by the bromination of allylamine (**1**), with *n*-BuLi. This cyclization required a lithium cation and seemed to proceed *via* two steps of cyclic transition states involving the intramolecular Br···Li$^+$ coordination. The resulting **ABB** was converted to **3** in three steps. These synthetic procedures will be easily scaled because chromatographical purification is unnecessary in each reaction.

Conclusions: We established the efficient synthetic method for **3** from **1** *via* **ABB**. This poster will discuss this synthetic route and the application of **ABB** to the synthesis of other useful azetidine derivatives.



P3E-V-014 Synthesis and antihypertensive activity evaluation of novel 2 -imidazolyl-substituted dihydropyridines

...n Hadizadeh[1,2], Zahra Fatehi-Hassanabad[5], Mohammad Bamshad[3], ...ed Poorsoghat[3], Ali Beheshtizadeh[3], Bibi Fatemeh Anaraki-Firooz[2]
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...ose: Numerous investigations are carried out to design novel drugs of ...ropyrine class with more selectivity and less adverse effects. The objective of the present study was to characterize the effects of a few ...ly synthesized dihydropyridine compounds with imidazolyl ...tuent at their 2 and 5 position of the ring on hypertensive rats. So a ... of dialkyl 1,4-dihydro-2-[2-(1-imidazolyl) ethyl]- 6-methyl-4-(1-...l-2-alkylthio-5-imidazolyl)-3,5-pyridinedicarboxylates (**3a-e**) were ...sized and their antihypertensive activities were determined on ...-salt induced hypertensive rats.

...od: First dialkyl 1,4-dihydro-2,6-dimethyl-4-(1-benzyl-2-alkylthio-5-...olyl)-3,5-pyridinedicarboxylates synthesized previously (**1a-e**) were ...d with paraformaldehyde and dimethylamine hydrochloride to give ... 1,4-dihydro-2-[2-(dimethylamino)ethyl]-6-methyl-4-(1-benzyl-2-...io-5-imidazolyl)-3,5-pyridinedicarboxylates (**2a-e**). Reaction of the ...with imidazole afforded the title dialkyl 1,4-dihydro-2-[2-(1-...olyl) ethyl]- 6-methyl-4-(1-benzyl-2-alkylthio-5-imidazolyl)-3,5-...edicarboxylates (**3a-e**). The antihypertensive activities of the ...diates (**1a-e**, **2a-c**) and title compounds (**3a-e**) were recorded in ...salt induced hypertensive rats through a direct measurement of ...blood pressure with indwelling catheter. A comparison was made ...fedipine.

All tested compounds were weaker compared to nifedipine but ...ective at doses below 1mg/kg, suggesting that they are effective as ...rtensive agents.

P3E-V-015 Synthesis and structure-activity studies on LY411575

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Purpose: Medium-sized lactams constitute an important class of structural motifs that can be widely found in many natural products and drugs. Development of an efficient tactic for the synthesis of medium-sized lactams and its application to the structure–activity studies on a potent γ-secretase inhibitor LY411575 have been investigated.

Methods: An intramolecular Staudinger–aza-Wittig (SAW) reaction of ω-azido pentafluorophenyl (pfp) ester was utilized as a potentially useful method for the synthesis of medium-sized lactams, which were elaborated into LY411575 by conventional chemistry. Inhibition of Aβ production by these analogues was evaluated in vitro using recombinant C-terminal fragment of APP as a substrate.

Results: An intramolecular SAW reaction of ω-azido pfp ester induced by the action of *n*-Bu_3P could be efficiently applied to the synthesis of 7- to 10-membered lactams. Elaboration of LY411575 analogues followed by evaluation of their ability to inhibit the Aβ production revealed that several new analogues were found to possess potent activity (IC_{50} 5.2–37 *n*M).

Conclusion: We have demonstrated that an intramolecular SAW reaction of ω-azido pfp ester is an efficient and general method for the construction of medium-sized lactams. Several new potent LY411575 analogues were synthesized by means of the present methodology.