ASYMMETRIC SYNTHESIS OF (*S*)-(+)- AND (*R*)-(-)-NZ-105 THROUGH THE MODIFIED MICHAELIS-ARBUZOV REARRANGEMENT AS A KEY STEP

Tatsuhisa KATO, Mamiko TEJIMA, Hirosato EBIIKE and Kazuo ACHIWA*
School of Pharmaceutical Sciences, University of Shizuoka 52-1 Yada, Shizuoka 422, Japan

The asymmetric synthesis of the (*S*)-(+)- and (*R*)-(-)-NZ-105 from the prochiral compound (**1**) was realized by using the modified Hunsdiecker reaction followed by the modified Michaelis-Arbuzov reaction with zerovalent palladium.

KEY WORDS 1,4-dihydropyridine; calcium antagonist; NZ-105; Hunsdiecker reaction; Michaelis-Arbuzov reaction

4-Aryl-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate derivatives show calcium antagonistic activity and are therapeutically useful vasodilators.[1] These calcium antagonists have a high affinity with the voltage-dependent calcium channel. Recently, a novel and structurally unique calcium antagonist (NZ-105 : 2-[Benzyl(phenyl)amino]ethyl 5-(5,5-Dimethyl-2-oxo-1,3,2-dioxaphosphorinane-2-yl)-1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3-pyridinecarboxylate) was prepared.[2,3] The very slow onset and recovery from NZ-105-induced vasodilation may be attributable to the slow and long-lasting inhibition of transmembrane calcium uptake which accompanies its very slow binding to and dissociation from DHP receptors.[4] Some of these 1,4-dihydropyridines have a chiral center at 4-position, and these enantiomers have been reported to show different biological activities; for example, (*S*)-NZ-105 exhibited no less than 850-fold calcium antagonistic activity compared with that of *R* isomer.[2] But these racemic 1,4-dihydropyridines have been used as vasodilators. NZ-105 so far has been synthesized as racemate[3] or has been enantiomerically synthesized with separation via diastereomeric ester[2] or chemoenzymatic separation.[5] We describe here the first asymmetric synthesis of (*S*)- and (*R*)-NZ-105, which includes a brominating process through the modified Hunsdiecker reaction and a coupling of the phosphorous to an sp^2 carbon atom.

The Michaelis-Arbuzov rearrangement,[6] also known as the Arbuzov reaction, is one of the most extensively investigated in organophosphorous chemistry and is widely used to prepare phosphonates, phosphinates and phosphine oxides.[7] To our knowledge, there is no report in the literature on a Michaelis-Arbuzov rearrangement applying to 1,4-dihydropyridines.

The difficulty of nucleophilic substitution at an sp^2 carbon atom by conventional organic techniques is overcome by using transition metals.[8] It has been reported that zerovalent palladium is an effective catalyst for cross-coupling of alkenyl halides with nucleophiles.[9] Adaptations of this palladium-catalyzed reaction to the Arbuzov reaction have also been reported.[10] The phosphorous-carbon bond formation by cross-coupling of alkenyl halides with the phosphite is one of the attractive and important pathways for the first asymmetric synthesis of NZ-105. We accomplished this type of the Arbuzov reaction with trialkyl phosphite, though the Arbuzov reactions in previous studies were carried out with dialkyl phosphite.

* To whom correspondence should be addressed.

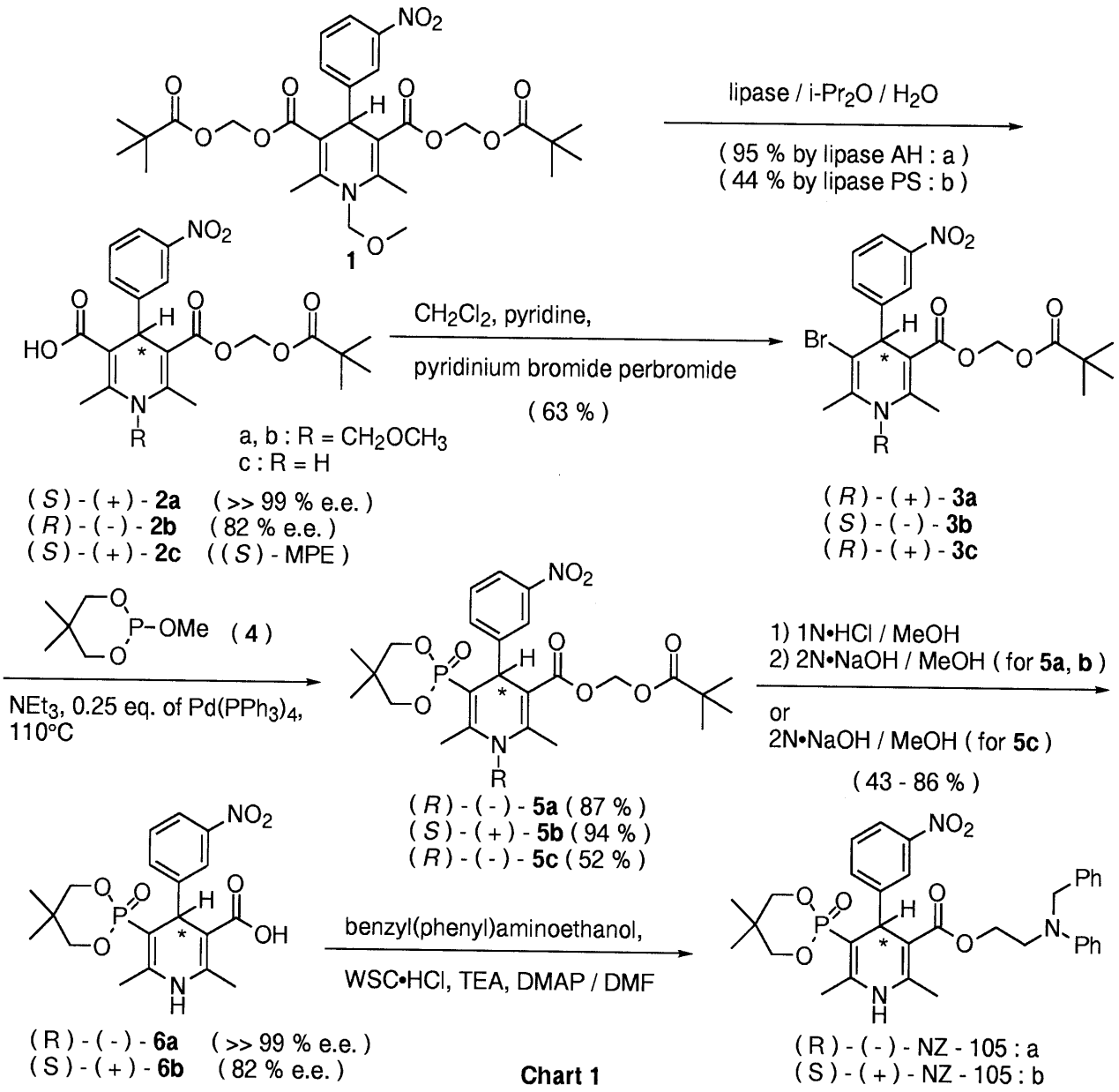

Chart 1

The prochiral compound (**1**) was hydrolyzed by lipase AH (*Pseudomonas sp.*), according to our previous report,[11] in diisopropyl ether saturated with water at room temperature (Chart 1) to give the optically active (*S*)-monocarboxylic acid (**2a**) in 95 % yield. (>> 99 % e.e. : Optical yield was determined by HPLC analysis after conversion into methyl ester.) Bromination of the monocarboxylic acid (**2a**) was carried out with pyridinium bromide perbromide in dichloromethane[12] at -20 °C to give the bromide (**3a**) in 63 % yield. Phosphination of the bromide (**3a**), as a key step, was carried out with the tri-alkyl phosphite (**4**) in the presence of tetrakis-triphenylphosphine palladium and triethylamine in toluene for 5 hours at 110 °C to give the product (**5a**) in 87 % yield. It was found that this reaction proceeded in good yield without racemization. Deprotection of the methoxymethyl group of **5a** with hydrochloric acid and the pivaloyloxymethyl group with sodium hydroxide gave the monocarboxylic acid (**6a**) in 86 % yield (>> 99 % e.e.) from **5a**. And the (*R*)- NZ-105 was obtained by esterification with the 2-

[benzyl(phenyl)amino]-ethanol in the presence of WSC according to our reported method. For the synthesis of the (*S*)-NZ-105, the prochiral compound (**1**) was hydrolyzed by lipase PS (*Pseudomonas sp.*) similarly to give the (*R*)-monocarboxylic acid (**2b**) in 44 % yield (82 % e.e.), which was then converted to (*S*)-NZ-105 by the same process as the synthesis of *R* isomer.

The commercially available monocarboxylic acid[13] (**2c** : (*S*)-monopivaloyloxymethyl ester : (*S*)-MPE) was also converted to the (*R*)-(-)- NZ-105 (Chart 1). Consequently, it was found that phosphination of the bromide (**3c**) with the trialkyl phosphite (**4**) catalyzed by tetrakis-triphenyl phosphine palladium proceeded to give the desired product (**5c**) in 52 % yield and the recovered bromide (**3c**) in 17 % yield without racemization. And hydrolysis of the (*R*)-**5c** gave the (*R*)-**6a** in 43 % yield.

By using the modified Hunsdiecker reaction with pyridinium ion and the Michaelis-Arbuzov rearrangement catalyzed by zerovalent palladium, the first asymmetric synthesis of both (*S*)-(+)- and (*R*)-(-)-NZ-105 was established.

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13) This compound **2c** was established the synthetic method in our labolatory and is produced by Amano Pharmaceutical Co., Ltd. using this method.; See reference 11).

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