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Lipase-catalyzed Asymmetric Hydrolysis and Regioselective Bromination of 1,4-Dihydropyridine. Synthesis of (*R*)-(+)-Nilvadipine

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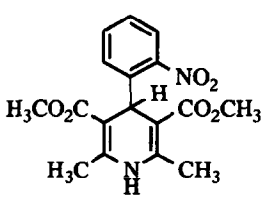
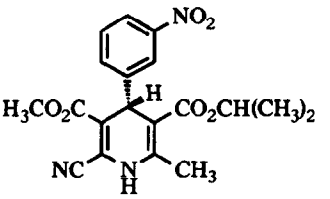
Abstract:: Homochiral (*R*)-(+)-nilvadipine was synthesized from a prochiral substrate using lipase-catalyzed asymmetric hydrolysis and subsequent regioselective bromination as key steps.

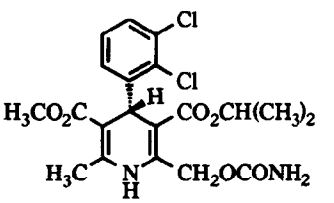
Calcium antagonists are investigated as antihypertensive drugs, especially 4-aryl-1,4-dihydropyridine-3,5-dicarboxylic acid diesters such as nifedipine,[1] NB-818,[2] and nilvadipine[3] have a high affinity with voltage-dependent calcium channel. Since the discovery of nifedipine in 1971, many 1,4-dihydropyridines have been widely investigated from the pharmacological point of view and some of them have been employed therapeutically. In the case of 1,4-dihydropyridines having different ester groups at C-3 and C-5 or different substituents at C-2 and C-6 possessing a stereogenic carbon at C-4, the two enantiomers were reported to show stereoselectivity of antagonism for the calcium channel.[4]



Nifedipine



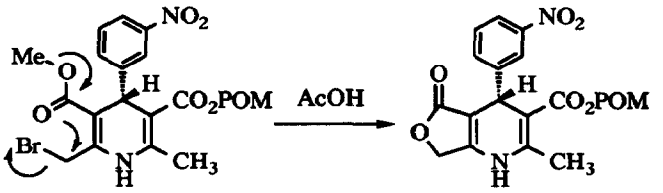
(*R*)-Nilvadipine



(*S*)-NB 818

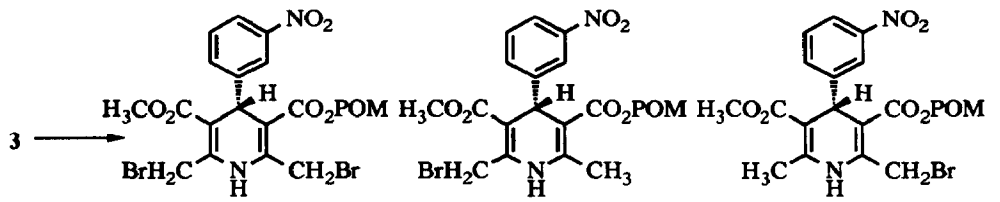
Recent studies have shown catalytic performance of enzymes for the preparation of enantiomerically pure compounds by asymmetric synthesis from prochiral compounds or kinetic resolution of racemic substrates.[5] We have already reported enzyme-catalyzed enantioselective syntheses of chiral 1,4-dihydropyridines in organic solvents.[6] In previous papers, [7] optically active 2-hydroxymethyl-1,4-dihydropyridines were also prepared from racemic substrates by using enzyme-catalyzed resolutions. However, the theoretical yields of kinetic resolution for one enantiomer are 50% at their best. In this paper, we will describe a method to brominate one of the two methyl groups of a 1,4-dihydropyridine ring regioselectively under mild conditions and enantioselective conversion of the 2-bromomethyl derivative into (*R*)-nilvadipine. We selected the bis(pivaloyloxymethyl) ester (**1**) as a substrate for enzyme-catalyzed enantioselective hydrolysis in an organic solvent according to our previous paper.[6] A mixture of **1** and lipase AH (*Pseudomonas sp.*) in diisopropyl ether (IPE) saturated with water was stirred for 35 hours at 25°C. The

hydrolysis proceeded to give almost nearly enantiomerically pure (93%ee) monocarboxylic acid (2) in high yield (83%) with only a very slight contamination. The optically active monocarboxylic acid (2) was treated with diazomethane in acetone at 0°C to afford 3, which was recrystallized from AcOEt/n-hexane to give homochiral 3 as pale yellow needles. Bromination of 3 was carried out with 4-dimethylamino-pyridinium bromoperbromide[8] in dichloromethane at -20°C. The reaction was followed by thin layer chromatography (TLC). After the substrate was consumed, the mixture was worked up. The ratio of bromides (**4a-c**) was determined by high performance liquid chromatography and the contaminants (**4a** and **4c**) were conveniently removed by medium pressure liquid chromatography. The structure of **4b** was confirmed by NMR spectrometry after conversion to the corresponding lactone by treatment of **4b** with acetic acid (Scheme 1).



4b **Scheme 1**

Table 1 Bromination of 3 with Bromoperbromide Salt [a,b,c]



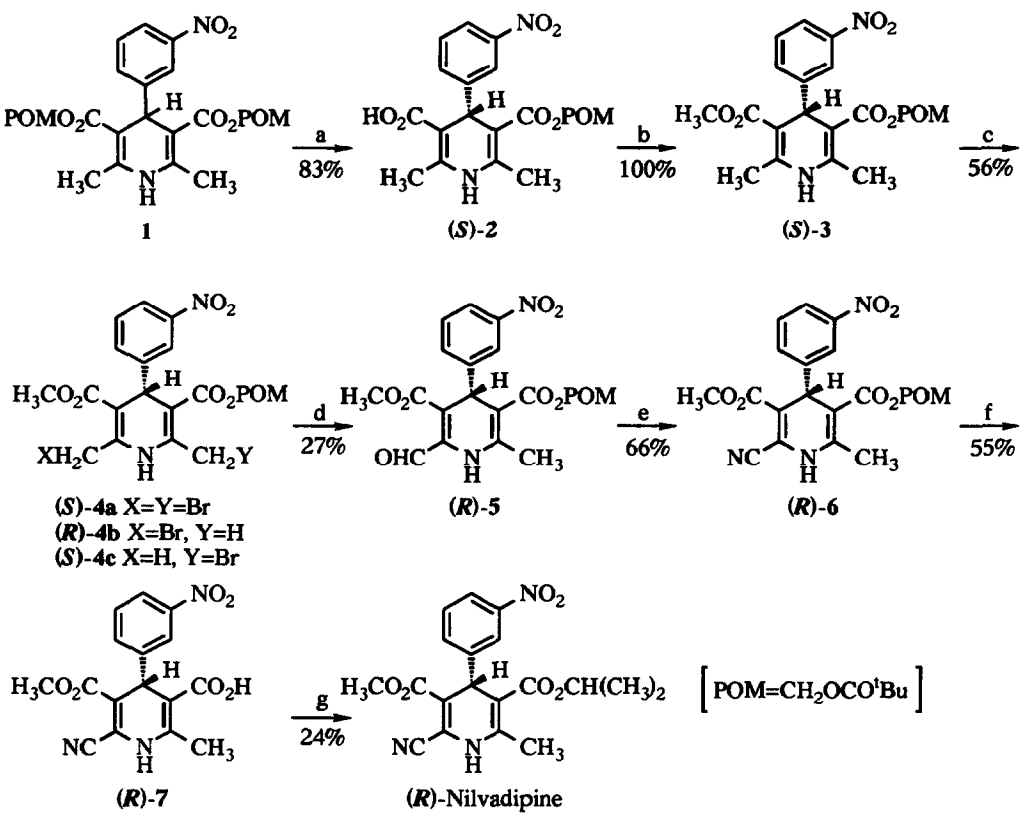
4a **4b** **4c**

Reagent	Time (h)	4a	4b	4c	Yield of 4b (%) [d]
1.5eq. DMAP•HBr•Br_2	3	1.1	7.3	1	56
2.2eq. DMAP•HBr•Br_2	3	34	1	0	trace
1.5eq. Pyridine•HBr•Br_2	3	0.7	6.5	1	65
1.7eq. Collidine•HBr•Br_2	5	1.7	8.9	1	56

a) All reactons were carried out by stirring a mixture of 3, 1.2eq. of pyridine and bromoperbromide salt in dichloromethane under argon atmosphere. *b)* Satisfactory elemental analyses of all products were obtained. *c)* The ratio of **4a-c** was measured by HPLC analysis using a column packed with YMC Pack SIL (2-propanol/n-hexane=1/20). *d)* Isolated yield.

Though bromination of 2- and 6-positions of 2,6-dimethyl-1,4-dihydropyridines was reported,[9] there is no report on regioselective bromination. The reaction conditions and results using other reagents, such as pyridinium bromoperbromide or collidinium bromoperbromide, were shown in Table 1. It seemed that the reagent tended to react from less hindered site and excessive reagent induced to form a dibromide (**4a**). These bromides (**4a-c**) were easily lactonized in solution even at 0°C.

The bromide[10] (**4b**) obtained was easily oxidized with dimethylsulfoxide in the presence of sodium bicarbonate to give an unstable aldehyde (**5**) which was purified by flash column chromatography. Treatment of **5** with hydroxylamine hydrochloride and acetic anhydride gave a cyano compound (**6**)[11], which was converted by removal of POM group into a monocarboxylic acid (**7**).[12,13] Esterification of **7** with thionyl chloride and 2-propanol yielded (*R*)-nilvadipine[12,14] (Scheme 2). We demonstrated the first asymmetric synthesis of (*R*)-nilvadipine, which is a derivative of unsymmetrically 2,6-substituted 2-cyano-6-methyl-1,4-dihydropyridine-3,5-dicarboxylic acid.



Reagents; a) lipaseAH/H_2O/IPE b) CH_2N_2/Acetone c) DMAP•HBr_3, Py/CH_2Cl_2 d) $NaHCO_3$/DMSO e) NH_2OH•HCl, Ac_2O, AcONa/AcOH f) KOH/MeOH g) $SOCl_2$, 2-Propanol

Scheme 2

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10. **4b**: $[\alpha]_D$ +40.0 (*c*2.5, acetone). ^{1}H-NMR ($CDCl_3$) δ: 1.12(9H, s, 3xCH_3), 2.42(3H, s, CH_3), 3.71(3H, s, OCH_3), 4.71(2H, s, CH_2Br), 5.14(1H, s, >CH-), 5.79(2H, ABq, J=5.5Hz, OCH_AH_BO), 7.17(1H, s, NH), 7.38-8.13(4H, m, C_6H_4).
11. **6**: $[\alpha]_D$ +179 (*c*0.74, acetone). IR (neat) 3308, 2236, 1760, 1719(cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 1.09(9H, s, 3xCH_3), 2.44(3H, s, CH_3), 3.79(3H, s, OCH_3), 5.19(1H, s, >CH-), 5.74(2H, ABq, J=5.5Hz, OCH_AH_BO), 6.55(1H, s, NH), 7.42-8.10(4H, m, C_6H_4). Positive FAB-MS m/z 458 $(M+1)^+$
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13. **7**: $[\alpha]_D$ +204 (*c*0.6, MeOH). IR (nujol) 3310, 2234, 1685(cm^{-1}). ^{1}H-NMR (Acetone-d_6) δ: 2.47(3H, s, CH_3), 3.75(3H, s, OCH_3), 5.24(1H, s, >CH-),7.56-8.16(4H, m, C_6H_4),9.14(1H, s, NH).
14. (***R***)-Nilvadipine: $[\alpha]_D$ +199 (*c*0.28, MeOH). IR (nujol) 3302, 2234, 1710(cm^{-1}). ^{1}H-NMR ($CDCl_3$) δ: 1.09(3H, d, J=6.2Hz, CH_3), 1.26(3H, d, J=6.2Hz, CH_3), 2.42(3H, s, CH_3), 3.78(3H, s, OCH_3), 4.91-5.01(1H, m, >CHO-), 5.18(1H, s, >CH-), 6.95(1H, s, NH), 7.42-8.17(3H, m, C_6H_3). The revised sequence rule of ***R,S***-nomenclature (Cahn, R. S. *J. Chem. Educ.*, **1964**, *41*, 508) indicated that (***S***)-nilvadipine[12] should be corrected to (***R***)-nilvadipine.

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