LIPASE AH-CATALYZED ASYMMETRIC SYNTHESIS OF (*S*)-(-)-NB 818

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Abstract - The first lipase-catalyzed asymmetric synthesis of biologically active (*S*)-(-)-NB818, has been achieved.

4-Aryl-1,4-dihydropyridine carboxylic diester derivatives are known as calcium channel blockers and the 1,4-dihydropyridine having different ester groups at 3 and 5 positions becomes chiral. The fact that there is a difference of pharmacological activity between the enantiomers has been reported by numerous investigators.[1]

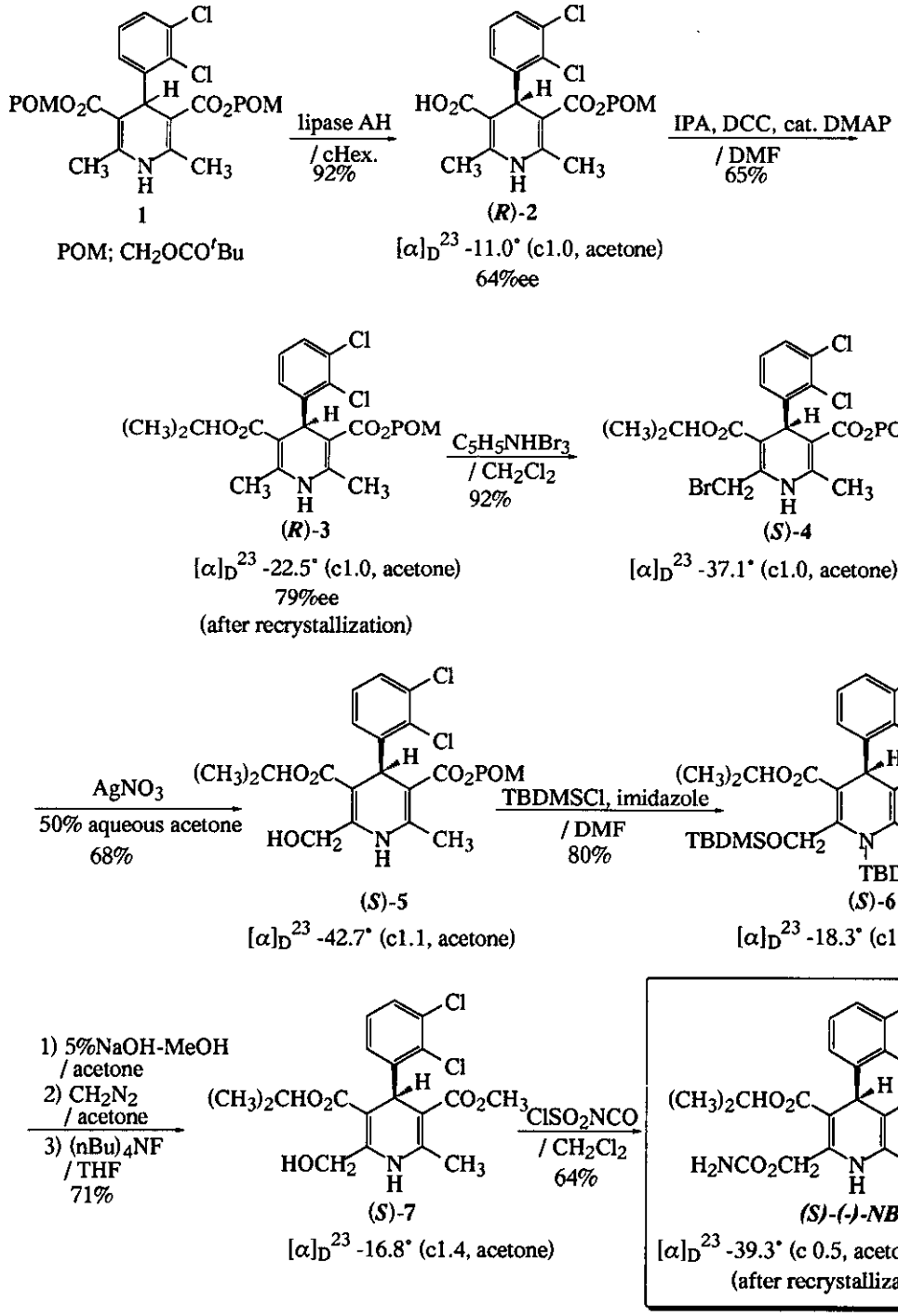
NB 818[2] is also one of those compounds whose (-)-form has stronger pharmacological activity than the (+)-form.[3] In a previous paper, we reported that the absolute configuration of pharmacologically active (-)-NB 818 was (*S*) by using chemical prooves.[4] So we carried out asymmetric synthesis of (*S*)-(-)-NB 818 by using lipase AH (*Pseudomonas sp.*)-catalyzed enantioselective hydrolysis.[5]

A mixture of **1** and lipase AH in cyclohexane (cHex.) saturated with water was stirred for 312 hours at room temperature. Hydrolysis proceeded to give the (-)-monocarboxylic acid (**2**) in high yield (92%). The absolute configuration of (-)-**2** was determined to be (*R*) by conversion to felodipine whose absolute configuration has already been determined by X-ray analysis.[6]

Esterification of (*R*)-(-)-**2** was carried out with isopropyl alcohol (IPA), dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-dimethylaminopyridine (DMAP) to give (*R*)-(-)-**3**. The enantiomeric purity of (*R*)-(-)-**3** was determined by hplc analysis to be 64%ee.[7] Compound ((*R*)-(-)-**3**) was recrystallized with diisopropyl ether (IPE) / hexane and the purity increased to 79%ee. Bromination of (*R*)-(-)-**3** was carried out with pyridinium bromide perbromide ($C_5H_5NHBr_3$) in dichloromethane at -20°C to give the monobromide ((*S*)-(-)-**4**) regioselectively because of the difference of steric hindrance between pivaloyloxymethyl ester and isopropyl ester. The structure of **4** was confirmed by nmr spectroscopy after conversion to the expected lactone (**8**)[8] by treatment with acetic acid (Scheme 1).[9] Compound ((*S*)-(-)-**4**) was reacted with $AgNO_3$ in 50% aqueous acetone to give the alcohol ((*S*)-(-)-**5**), followed by protection with *tert*-butyldimethylchlorosilane (TBDMSCl) to give (*S*)-(-)-**6**. The mono-pivaloyloxymethyl ester ((*S*)-(-)-**6**) was hydrolyzed with 5%NaOH-methanol and esterified with diazomethane to give the methyl ester.

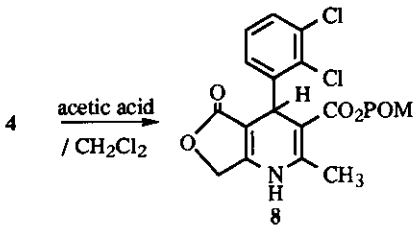
Deprotection of the silylated methyl ester with tetrabutylammonium fluoride gave (*S*)-(-)-**7**.[10]

Lipase-catalyzed Asymmetric Synthesis of (S)-(-)-NB818



Alcohol ((*S*)-(-)-**7**) was reacted with chlorosulfonyl isocyanate ($ClSO_2NCO$) at -20°C to afford (*S*)-(-)-NB 818.[11] This (*S*)-(-)-NB 818 was recrystallized with IPE/ hexane and the purity became 95%ee.[12]

Scheme 1.



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6. B. Lamm, R. Simonsson, and S. Sundell, *Tetrahedron Lett.*, 1989, **30**, 6423.
7. Determined by using CHIRALPAK AS (n-hexane/ 2-propanol= 30/ 1).
8. 8: ^{1}H-Nmr (DMSO-d_6) δ: 0.97 (9H, s, $3CH_3$), 2.33 (3H, s, CH_3), 4.84 (2H, s, CH_2O), 5.26 (1H, s, >CH-), 5.45 (2H, ABq, J=5.8 Hz, OCH_AH_BO), 7.24-7.43 (3H, m, C_6H_3).
9. H. Ebiike and K. Achiwa, *Tetrahedron: Asymmetry*, 1994, **5**, 1447.
10. When racemic **6** was hydrolyzed, there were a few deprotected compounds. So (*S*)-(-)-**6** was converted to (S)-(-)-**7** without isolation of the intermediates.
11. (*S*)-(-)-NB818: Ir (nujol) 3342, 1686, 1606 (cm^{-1}). ^{1}H-Nmr ($CDCl_3$) δ: 1.02 (3H, d, J=6.2 Hz, CH_3), 1.26 (3H, d, J=6.2 Hz, CH_3), 2.30 (3H, s, CH_3), 3.62 (3H, s, CH_3O), 4.92-5.02 (1H, m, >CH-), 5.30 (2H, ABq, J=14.4 Hz, CH_AH_BO), 5.46 (1H, s, >CH-), 7.05-7.31 (3H, m, C_6H_3).
12 Determined by using CHIRALPAK AS (n-hexane/ 2-propanol= 3/ 1).

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