

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

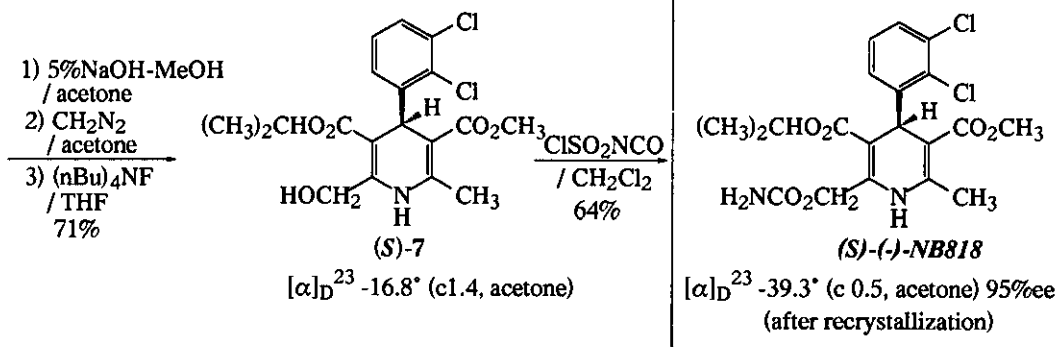
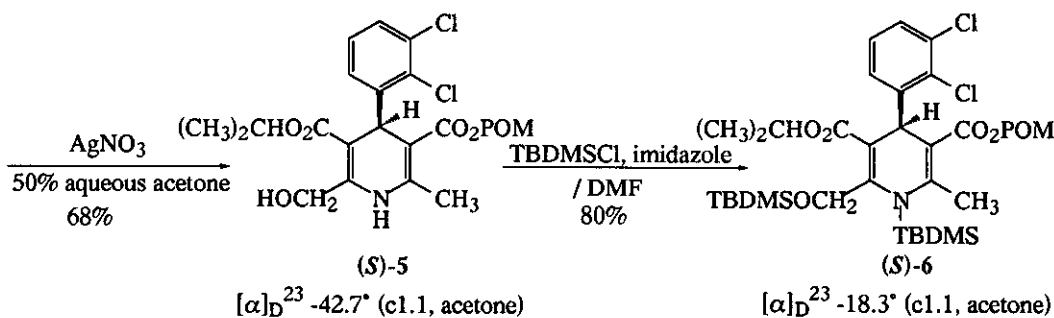
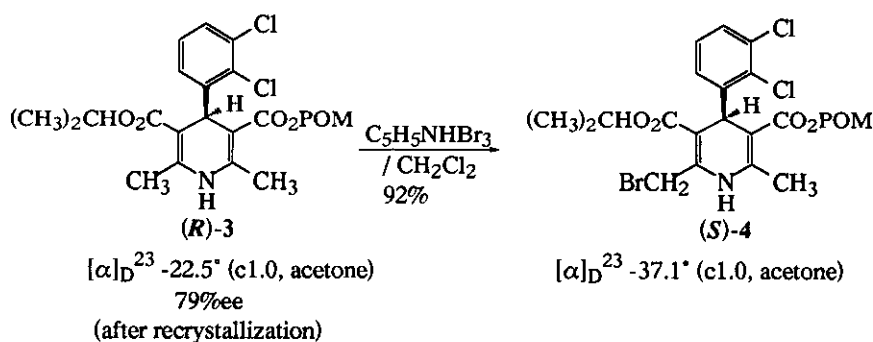
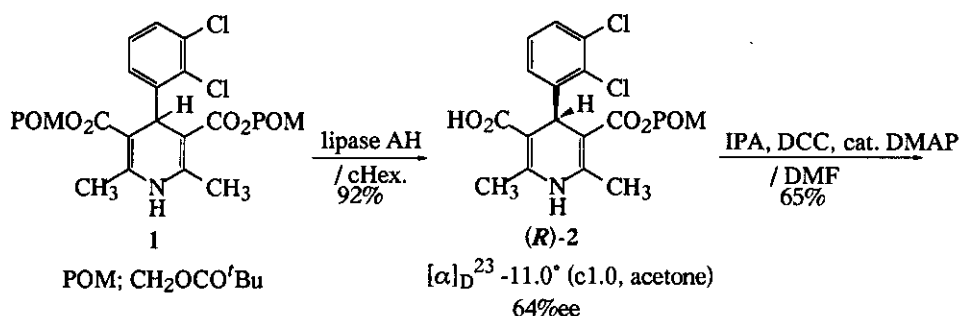
NB 818² is also one of those compounds whose (-)-form has stronger pharmacological activity than the (+)-form.³ In a previous paper, we reported that the absolute configuration of pharmacologically active (-)-NB 818 was (S) by using chemical proves.⁴ So we carried out asymmetric synthesis of (S)-(-)-NB 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 (C₅H₅NHBr₃) 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 AgNO₃ 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.

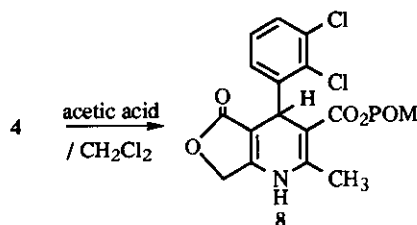
Deprotection of the silylated methyl ester with tetrabutylammonium fluoride gave (S)-(-)-7.¹⁰

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



Alcohol ((S)-(-)-7) was reacted with chlorosulfonyl isocyanate (ClSO₂NCO) 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.



REFERENCES AND NOTES

1. F. Bossert, F. Meyer, and E. Wehinger, *Angew. Chem. Int. Ed. Eng.*, 1981, **20**, 762.
2. M. Nishikibe, *J. Pharmacol. Exp. Ther.*, 1988, **246**, 719.
3. T. Nakazawa, Y. Fukuta, Y. Tanaka, K. Ishii, and K. Nakayama, *Folia Japonica*, 1994, **103**, 47.
4. Y. Yamazaki, H. Ebiike, and K. Achiwa, *Chem. Pharm. Bull.*, 1994, **42**, 1968.
5. Many enzymatic reactions were applied to enantioselective synthesis. Recent reviews see: E. Santaniello, P. Ferraboschi, P. Grisenti, and A. Manzocchi, *Chem. Rev.*, 1992, **92**, 1071. M. Murata, H. Ebiike, and K. Achiwa, *Journal of Synthetic Organic Chemistry, Japan*, 1991, **49**, 1127. E. Mizuguti, H. Nagai, H. Uchida, and K. Achiwa, *Journal of Synthetic Organic Chemistry, Japan*, 1994, **52**, 638.
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. ¹H-Nmr (DMSO-d₆) δ: 0.97 (9H, s, 3CH₃), 2.33 (3H, s, CH₃), 4.84 (2H, s, CH₂O), 5.26 (1H, s, >CH-), 5.45 (2H, ABq, J=5.8 Hz, OCH₂CH₂O), 7.24-7.43 (3H, m, C₆H₃).
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). ¹H-Nmr (CDCl₃) δ: 1.02 (3H, d, J=6.2 Hz, CH₃), 1.26 (3H, d, J=6.2 Hz, CH₃), 2.30 (3H, s, CH₃), 3.62 (3H, s, CH₃O), 4.92-5.02 (1H, m, >CH-), 5.30 (2H, ABq, J=14.4 Hz, CH₂CH₂O), 5.46 (1H, s, >CH-), 7.05-7.31 (3H, m, C₆H₃).
12. Determined by using CHIRALPAK AS (n-hexane/ 2-propanol= 3/ 1).

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