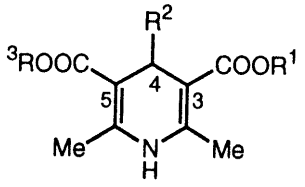
NOVEL AND CHIRAL HANTZSCH-TYPE 1,4-DIHYDROPYRIDINES HAVING A *p*-TOLYLSULFINYL GROUP. SYNTHESIS AND BIOLOGICAL ACTIVITIES AS CALCIUM CHANNEL ANTAGONISTS

Kazuyuki MIYASHITA, Masahiro NISHIMOTO, Tetsuya ISHINO, Satoshi OBIKA, and Takeshi IMANISHI*
Faculty of Pharmaceutical Sciences, Osaka University, Yamadaoka 1-6, Suita, Osaka 565, Japan

Both C-4 stereoisomers of novel Hantzsch-type 4-aryl- and 4-methyl-1,4-dihydropyridines **3** having a *p*-tolylsulfinyl group at C-5 were efficiently synthesized in optically pure forms starting from the α-sulfinyl enones **6** which could be easily obtained from (–)-menthyl (*S*)-*p*-tolylsulfinate (**4**). The stereochemistry at C-4 was found to be largely responsible for the biological activities as calcium channel antagonists of these compounds.

KEY WORDS Hantzsch-ester; 1,4-dihydropyridine; *p*-tolylsulfinyl group; synthesis; optically active form; calcium channel antagonist

The Hantzsch-esters, 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylates **1**, are very attractive compounds from the standpoint of their outstanding biological activities. The 4-aryl-1,4-dihydropyridine derivatives are well known to be highly effective calcium channel antagonists. [1] In addition, it was recently reported that the 4-methyl-1,4-dihydropyridines interfered with platelet aggregation, without any cardiovascular effects. [2] In these 4-substituted-1,4-dihydropyridines **1**, the C-4 position becomes stereogenic when R^1 and R^3 are different. Since configuration is known to be so closely related to biological activities, [1b, 3] it is of great value to synthesize each enantiomer in a stereoselective fashion. [4,5]



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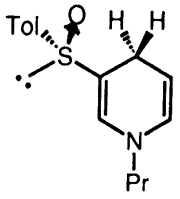

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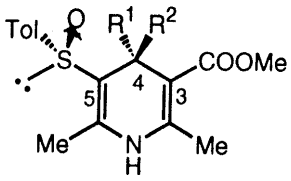


3Aa: R^1= Ph, R^2= H
b: R^1= *o*-Cl-Ph, R^2= H
c: R^1= Me, R^2= H
3Ba: R^1= H, R^2= Ph
b: R^1= H, R^2= *o*-Cl-Ph
c: R^1= H, R^2= Me

In our previous study of the NADH model compound **2**, the extraordinarily high effectiveness of a chiral sulfinyl group for asymmetric reduction has become clear. [6] Now, by combination of compounds **1** and **2**, we have designed the novel classes of optically active Hantzsch-type compounds, 4-aryl- and 4-methyl-1,4-dihydropyridines **3**, which are very interesting from the viewpoint of both biological and chemical properties. In this paper, we wish to describe the versatile syntheses of **3**, and also report their activities as calcium channel antagonists.

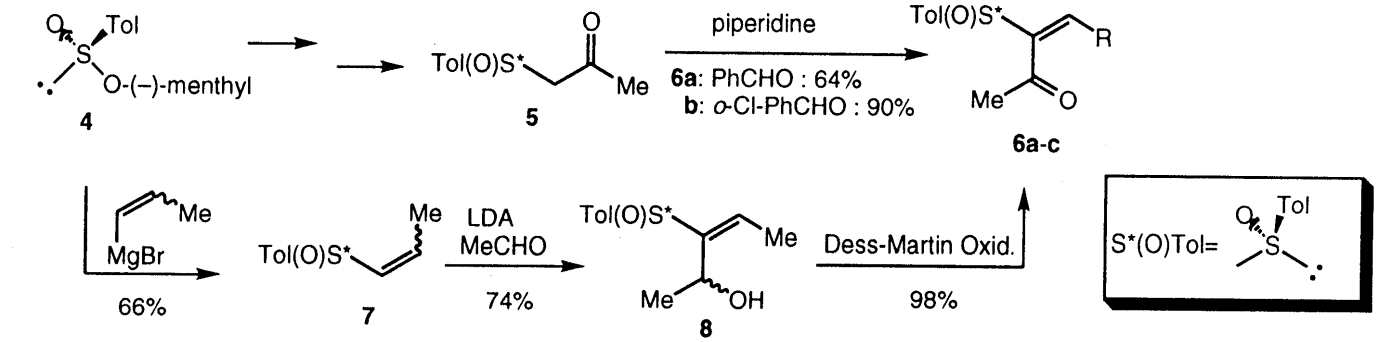
The keto sulfoxide **5**, [7] easily obtained from (-)-menthyl (*S*)-*p*-tolylsulfinate (**4**), [8] was condensed with arylaldehydes under modified Knoevenagel conditions [9] to give the enones **6a,b** in good yields. Enone **6c** was also prepared *via* an alternative route. The reaction of **4** with 1-propenylmagnesium bromide in THF afforded **7** as a mixture of two isomers (*E*:*Z* = *ca.* 1:3) in 66% yield. [10] Lithiation of **7** and the subsequent treatment with an excess of acetaldehyde gave **8** as a 1:1 diastereoisomeric mixture in 74% yield. [11] On oxidation with the Dess-Martin periodinane, [12] **8** produced the enone **6c** in an excellent yield.

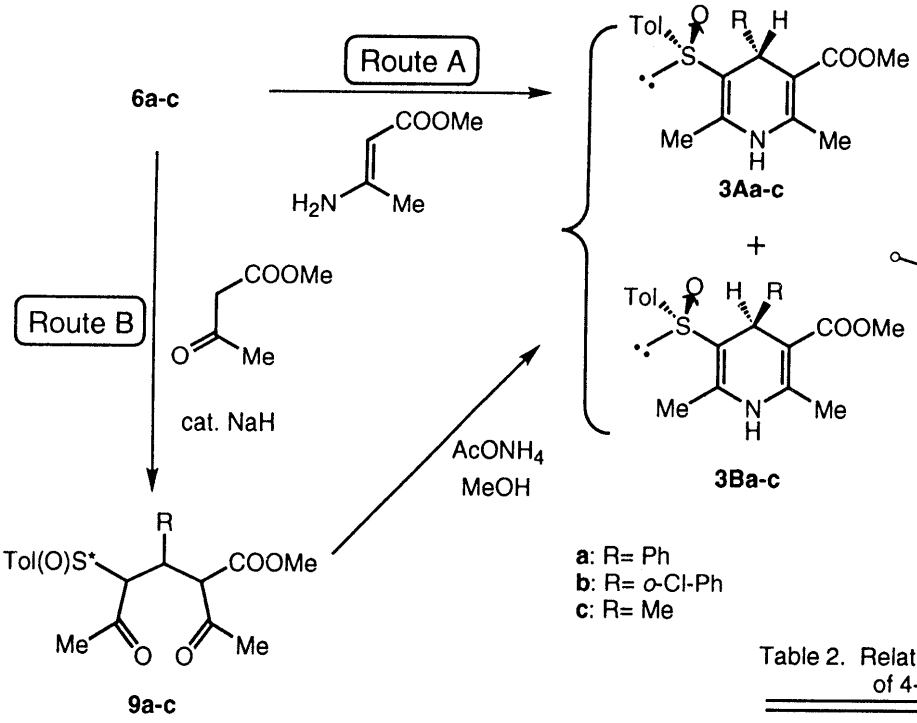
The reaction of **6a,b** with methyl 3-aminocrotonate in the presence of a catalytic amount of magnesium perchlorate in 2,2,2-trifluoroethanol at room temperature (Route A) gave the corresponding 4-aryl-1,4-dihydropyridines **3Aa,b** both as single diastereomers. [5,13] A similar treatment of **6c** in methanol without the catalyst also gave a satisfactory result (Table 1). [14, 15]

On the other hand, **6a-c** were treated with methyl acetoacetate in the presence of sodium hydride to give the corresponding diketones **9a-c**, which were condensed with ammonium acetate in methanol to afford the desired products **3Aa-c** and **3Ba-c** (Route B). [15,16] It is quite noteworthy that the stereoselectivity of the products (**3Aa,b** / **3Ba,b**) in Route B is opposite to that in Route A. This phenomenon means that both diastereomers in the case of 4-aryl derivatives are obtainable selectively by use of Route A or Route B, although there has been no reasonable explanation for the reverse stereoselectivity.

* To whom correspondence should be addressed.

The stereochemistries of these products **3A** and **3B** were confirmed on the basis of X-ray crystallographic analysis and ^{1}H-NMR data.[16] As shown in Fig. 1, the X-ray structure of **3Bb** indicates that the lone pair on the sulfur atom of the sulfinyl group is proximal to the methyl group at C-6 as expected from consideration of the allylic 1,3-strain.[18] The differences in the chemical shifts of the hydrogens at C-4 between **3Aa**,**b**,**c** (4.86, 5.47 and 3.83 ppm) and **3Ba**,**b**,**c** (4.51, 4.92 and 3.37 ppm) are attributable to the deshielding effect of the neighboring oxygen atom of the sulfinyl group in **3A** and the shielding effect of the neighboring tolyl group in **3B**, respectively.





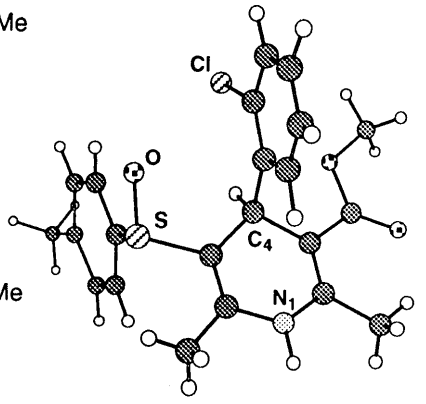


Fig. 1. 3-D Representation of **3Bb**

Table1. Cyclization of **6** to 1,4-Dihydropyridines **3**

Compd.	Route A			Route B	
	Conditions	Yield (%)	**3A**:**3B**	Yield [a] (%)	**3A**:**3B**
a: R= Ph	*b*)	55	1 : 0	43	1 : 1.5
b: R= *o*-Cl-Ph	*b*)	45	1 : 0	41	1 : 2
c: R= Me	*c*)	80	2.5 : 1	54	1.7 : 1

a) Overall yield from **6**. *b*) In the presence of 0.5eq of $Mg(ClO_4)_2$ in 2,2,2-trifluoroethanol at room temperature. *c*) In methanol at room temperature.

Table 2. Relative Vasorelaxant Activities of 4-Aryl-1,4-dihydropyridines

Compd.	Conc. (nM)	Relative activity (%)
Nifedipine	1	100
3Aa	10	10
3Ab	10	29
3Ba	1	24
3Ba	10	69
3Bb	1	50
3Bb	10	69

Relative vasorelaxant activities of thus obtained 1,4-dihydropyridines are summarized in Table 2, which shows that the **3B**-type stereoisomers are much more effective than the **3A**-type ones and compound **3Bb** has the highest activity (1/2 of nifedipine) among these compounds. These results indicate the potential effectiveness of this type of compound having a sulfinyl group as a calcium channel antagonist.

Application of these novel 1,4-dihydropyridines for asymmetric reductions is now in progress.

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14) The reaction of **6c** with methyl 3-aminocrotonate in the presence of magnesium perchlorate in 2,2,2-trifluoroethanol gave only a complex mixture of products.

15) Optical purities of these compounds were determined on the basis of ^{1}H-NMR analysis by use of a chiral shift reagent, Eu(tfc)$_3$ or (*R*)-*N*-3,5-dinitrobenzoyl-α-phenylethylamine[17] and were almost 100%.

16) **3Aa**, mp 212-213°C(MeOH). $[\alpha]_D^{22}$ +140.2° (*c*=0.54, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.19, 2.29, 2.44, 3.57 (each 3H, s), 4.86 (1H, s), 5.73 (1H, br s) , 6.72-7.07 (9H, m). **3Ba**, mp 176-177°C (benzene-hexane). $[\alpha]_D^{21}$ +518.8° (*c*=0.63, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.23, 2.30, 2.40, 3.47 (each 3H, s), 4.51 (1H, s), 6.56 (1H, br s), 7.10-7.43 (9H, m). **3Ab**, mp 199-200°C (MeOH). $[\alpha]_D^{22}$ +141.5° (*c*=0.51, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.17, 2.31, 2.39, 3.53 (each 3H, s), 5.47 (1H, s), 6.68-7.17 (9H, m). **3Bb**, mp 139-141°C (ethyl acetate). $[\alpha]_D^{22}$ +464.5° (*c*=0.64, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.18, 2.25, 2.42, 3.46 (each 3H, s), 4.92 (1H, s), 6.95-7.51 (9H, m). **3Ac**, mp 186-187°C (Et_2O-$CHCl_3$). $[\alpha]_D^{23}$ +542.5° (*c*=1.03, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 0.25 (3H, d, *J*=6 Hz), 2.25, 2.31, 2.39, 3.65 (each 3H, s), 3.83 (1H, q, *J*=6 Hz), 7.21 (1H, br s), 7.28, 7.51 (4H, AA'BB', *J*=8 Hz). **3Bc**, mp 173-174°C (ethyl acetate). $[\alpha]_D^{23}$ +473.3° (*c*=1.07, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, *J*=6 Hz), 2.25, 2.33, 2.38 (each 3H, s), 3.37 (1H, q, *J*=6 Hz), 3.53 (3H, s), 6.76 (1H, br s), 7.25, 7.43 (4H, AA'BB', *J*=8 Hz).

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