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ENANTIOSELECTIVE HANTZSCH DIHYDROPYRIDINE SYNTHESIS VIA METALATED CHIRAL ALKYL ACETOACETATE HYDRAZONES[1]

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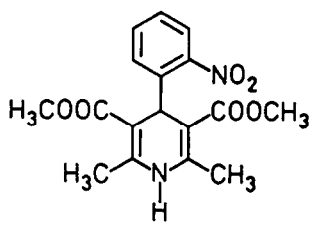
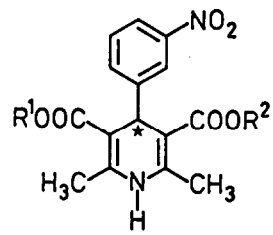
Summary: An efficient, overall enantioselective variant of the Hantzsch synthesis of 4-aryl-1,4-dihydropyridines 5 (ee = 84 - 98%), important biologically active compounds (e. g. as calcium channel blockers), is described. Key step of the new procedure is the asymmetric Michael addition of metalated chiral alkyl acetoacetate hydrazones (S)-2 to the Knoevenagel acceptors 4. An accurate method to determine the enantiomeric excess of chiral dihydropyridines is also reported.

Since their discovery by Hantzsch more than 100 years ago[2], 1,4-dihydropyridine (DHP) derivatives[3] have gained much interest as coenzymes in dehydrogenases (NAD(P)H)[4], as intermediates in alkaloid synthesis[5], and because of the broad spectrum of their biological activities[3]. Of special importance is their use as potent calcium channel blockers[6]; for instance, nifedipine® A is used clinically against angina pectoris and hypertension. Unsymmectrically substituted 4-aryl-1,4-dihydropyridines, such as nitrendipine® B (R^1=CH_3, R^2=C_2H_5)[7], are chiral and exist as two enantiomers. As expected, the biological activities of such DHP enantiomers are different [6b,8], culminating in recent reports of opposite activity (Ca^{2+} antagonist and Ca^{2+} agonist)[9]. Thus, enantioselective syntheses of chiral 4-aryl-1,4-dihydropyridines are highly desirable [10].

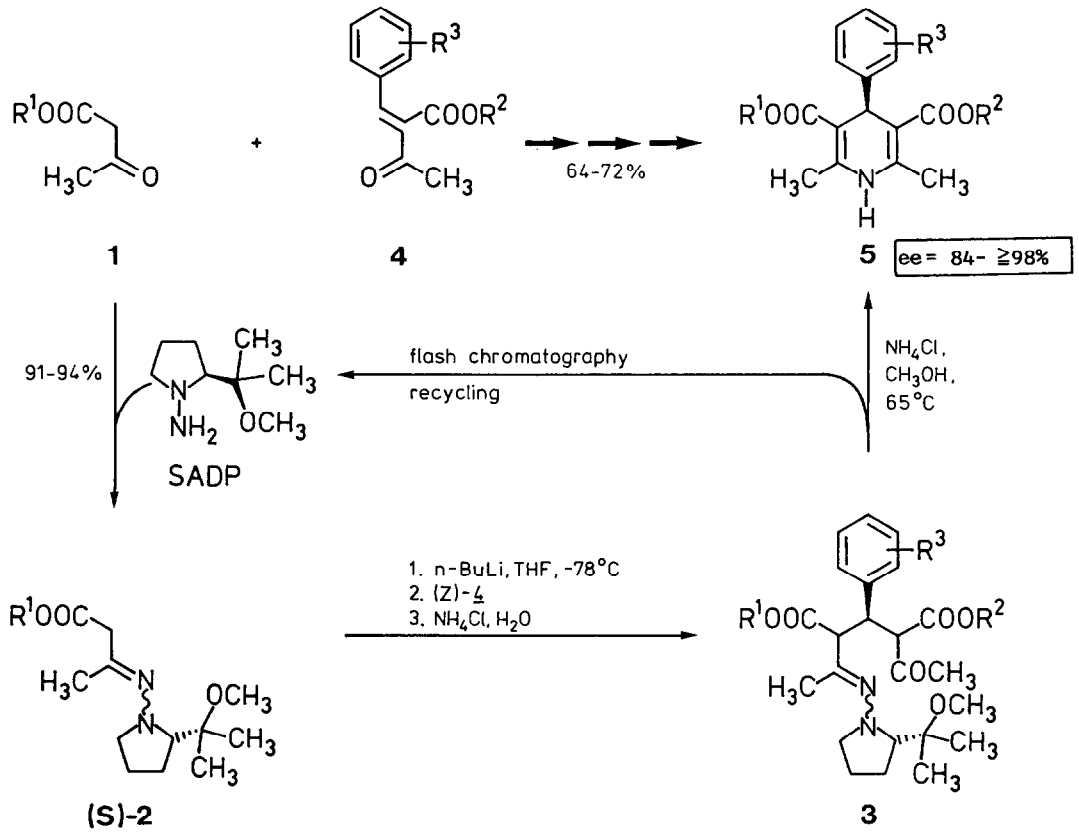


A



B

We now describe an efficient asymmetric synthesis (overall yields: 64-72%, ee = 84-≥98%) of DHP derivatives 5. In contrast to the techniques used previously [6b,7-10], in our new enantioselective Hantzsch variant the chirality information is introduced via the nitrogen functionality.



As shown in the scheme, alkyl acetoacetates 1 are condensed with the chiral hydrazine (S)-(-)-1-amino-2-(dimethylmethoxymethyl)pyrrolidine (SADP)[11] to the corresponding SADP-hydrazones (S)-2, which mainly exist as their tautomeric enehydrazines (NMR, IR). After metalation with n-butyllithium (THF, -78°C, 10 min) and subsequent dropwise addition of the acceptors (Z)-4 [12] (dissolved in THF), the reaction mixture is stirred for 1 h at -78°C and then worked up (aqueous NH_4Cl/ether) affording the Michael adducts 3[13]. Refluxing of the crude adducts in MeOH/aqueous NH_4Cl solution at 65°C for 1 h releases the chiral auxiliary SADP and effects ring closure to the dihydropyridines 5, which are purified by flash chromatography (recycling of the chiral auxiliary).

The enantiomeric purity of the DHP derivatives 5 was determined by ^1H NMR-LIS technique (on the methyl singlets at 2- and 6-position) and by HPLC using β-cyclodextrin as chiral stationary phase [14](see figure and table). The absolute configurations given are based on the correlation of polarimetric data (see table) and assuming a uniform mechanism for all 1.4-additions according to the general scheme. Both enantiomers of the chiral DHP's 5 may be obtained at will by either changing the chiral auxiliary from SADP to its

antipode RADP (see 5d) or by simply changing the groups R^1 and R^2 of the acceptor and chiral nucleophile respectively (see 5c, synthon control of enantioselectivity).

Our recent findings that other acceptors of type 4 bearing a nitro or an acetyl group instead of the ester function, can also be used successfully, indicate a broad applicability of this novel asymmetric Hantzsch DHP synthesis[15].

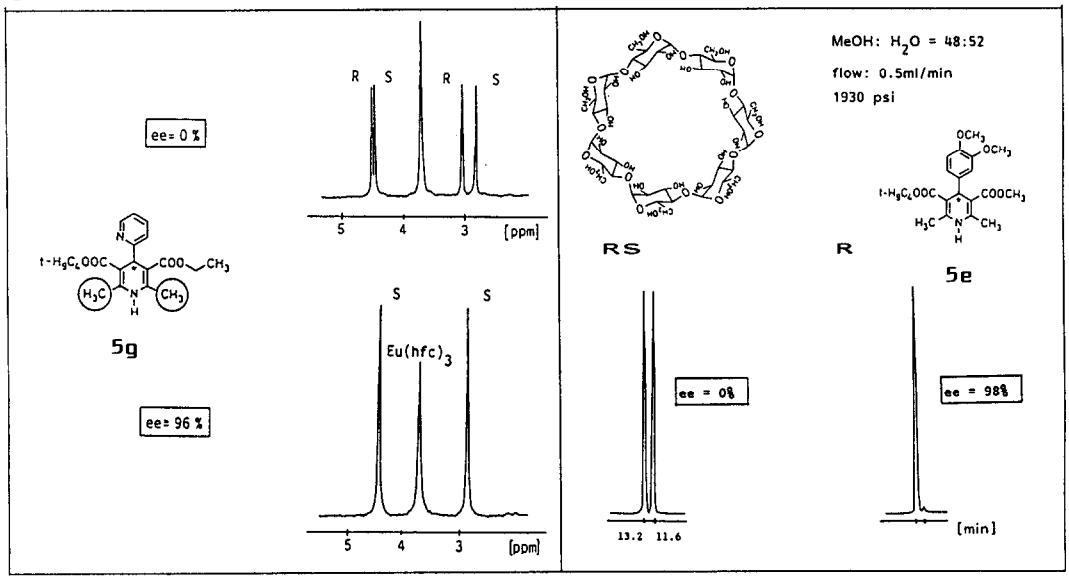


Figure. Determination of enantiomeric excess of DHP derivatives 5 by ^{1}H NMR-LIS and HPLC-CSP technique.

Table. Highly enantiomerically enriched 4-aryl-1,4-dihydropyridines 5 prepared by asymmetric synthesis via SADP-/RADP-hydrazones.

5	R^1	R^2	R^3	overall yield [%]	m.p. [°C]	$[\alpha]_D^{25}$ [°] (c,acetone)	ee[a] [%]	confg.[b]
a	C_3H_5	C_2H_5	H	69	105	+29.4 (1.1)	84	(S)
b	CH_3	i-C_3H_7	3,4-OCH_2O	71	130	+ 6.5 (1.3)	85	(R)
c	t-C_4H_9	$H_3CO(CH_2)_2$	3,4-OCH_2O	67	134	-17.0 (1.0)	94	(S)
c	$H_3CO(CH_2)_2$	t-C_4H_9	3,4-OCH_2O	67	134	+17.4 (1.0)	≥96	(R)
d	t-C_4H_9	C_2H_5	4-CH_3	64	140	+12.9 (1.0)	92	(S)
d	t-C_4H_9	C_2H_5	4-CH_3	65	140	-12.4 (1.0)	91	(R)[c]
e	t-C_4H_9	CH_3	3,4-$(OCH_3)_2$	72	144	+14.4 (1.0)	98	(S)
f	t-C_4H_9	C_2H_5	3,4,5-$(OCH_3)_3$	70	152	+11.3 (1.0)	≥96	(S)
g	t-C_4H_9	C_2H_5	2-pyridyl	64	185	+ 2.0 (1.0)	≥96	(S)

a) Determined by ^{1}H NMR-LIS (90 MHz, $CDCl_3$) or by HPLC-CSP (see figure).
b) Using our new procedure (SADP auxiliary) we prepared dihydropyridines (+)-B (R^1=CH_3, R^2=i-C_3H_7 and R^1=C_2H_5,R^2=i-C_3H_7); thus, we assign the (R)-configuration, if R^2>R^1 [16]. c) RADP was used as chiral auxiliary.

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