ASYMMETRIC ELECTROPHILIC α-AMIDOALKYLATION 6[1]: SYNTHESES OF TETRAHYDROISOQUINOLINES OF HIGH ENANTIOMERIC PURITY.

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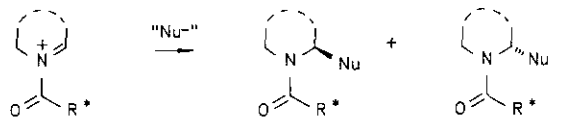
Abstract - Syntheses of 1-substituted tetrahydroisoquinolines of high enantiomeric purity are described. As key step a diastereoselective trapping reaction of a chiral acyliminium ion with silyl enol ethers is involved. The starting acyliminium ion can be prepared by hydride abstraction with triphenylcarbonium tetrafluoroborate.

There are at present several different methods for preparing 1-substituted 1,2,3,4-tetrahydroisoquinolines in enantiomerically pure form. They are based on resolution, enantioselective catalytic hydrogenation, diastereoselective alkylation of chiral formamidine derived anions and on the incorporation of carbon fragments derived from the chiral pool. A survey of these methods has been provided in a recent paper[2]. The interest in tetrahydroisoquinolines is due to their wide distribution among both alkaloids[3] and biologically active compounds of synthetic origin[4].



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We have now found a novel method for the synthesis of α-substituted amines in optically pure form that we have termed asymmetric electrophilic α-amidoalkylation (AEαA). The trapping reaction of a chiral acyliminium ion (R*CO= chiral auxiliary in 1), which represents an asymmetric electrophilic α-amidoalkylating agent, with a nucleophile ("Nu⁻") was expected to proceed with stereoselective bond formation. As a result thereof one diastereomer (2 or 3) should predominate which after purification to a single diastereomer and subsequent removal of the chiral

auxiliary would yield an enantiomerically pure amine. This plan has been successfully implemented with pyrrolidines[5] and piperidines[6].

In this communication we wish to report the extension of this concept to the synthesis of tetrahydroisoquinolines.

First there was need for an efficient method for generating the acyliminium ion 6. Hydride abstraction[7] from 4 seemed to be the most direct route. Upon treatment of amide 4 with triphenylcarbonium tetrafluoroborate 5 at room temperature (in CH_2Cl_2) the starting material was indeed completely consumed within 16 h and a yellow precipitate formed.

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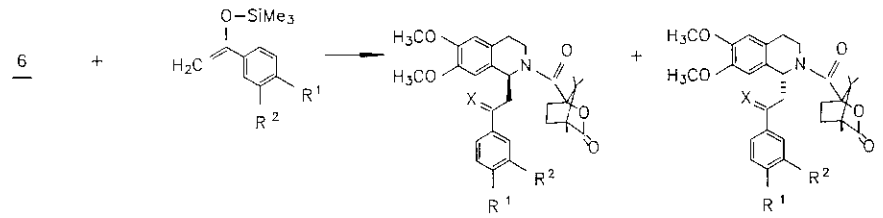


8 (S)-9 X=O (S)-11 X=H_2 (R)-10 X=O (R)-12 X=H_2

Addition of extra solvent resulted in a clear yellow solution to which enol ether 8a (1.2 eq. in CH_2Cl_2) was added at -78°C. After workup a mixture of diastereomers (S)-9a and (R)-10a was obtained. On SiO_2 no separation of (S)-9a from (R)-10a could be effected although various solvents were employed. The composition of the diastereomeric mixture was determined as 20.3/79.7 by HPLC using a chiral stationary phase[8] (see Table 1). The reaction also proceeded smoothly at -90°C. Thereby the (S)-9a/(R)-10a ratio was improved to 17.6/82.4 and the mixture of diastereomers was obtained in a combined yield of 97.2%. An even more stereoselective reaction could be brought about by adding $TiCl_4$ (1 eq. at -78°C) prior to the addition of silyl enol ether 8a. In this case at -78°C and -93°C (temp. of enol ether addition) diastereomeric ratios of 12.4/87.6 and 11.2/88.8 (Table 1, entries 3 and 4), respectively, could be achieved. The results of the bond forming

reactions (at -78°C, without $TiCl_4$) with silyl enol ethers 8b and 8c can be taken from Table 1. In these cases the influence of lower temperatures and $TiCl_4$ has not been investigated yet.

Table 1.

entry	8	R^1	R^2	Reaction cond. Add.	Temp.[°C]	Yield [%] (S)-9+(R)-10	Ratio (S)-9/(R)-10	Ratio (S)-11/(R)-12	(R)-12 Yield [%][a]	(R)-12 $[\alpha]_{578}$
1	a	H	H		-78	---	20.3/79.7	---	---	---
2	"	"	"		-90	97.2	17.6/82.4	16.7/83.3	59.1	-119.6°
3	"	"	"	1 eq.$TiCl_4$	-78	---	12.4/87.6	---	---	---
4	"	"	"	1 " "	-93	---	11.2/88.8	---	---	---
5	b	H	Cl		-78	98.9	14.8/85.2	9.9/90.1	5.3[b] 51.9[c]	-102.9°
6	c	OCH_3	OCH_3		-78	96.8	17.6/82.4	18.5/81.5	37.8	- 83.0°

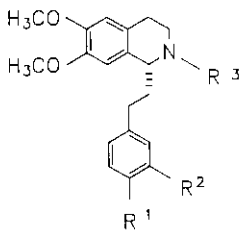
a) Pure compound according to HPLC. b) Pure compound for analytical purposes only. c) Hard to separate mixture of (R)-12a and (R)-12b.

Compounds (S)-9/(R)-10 a-c have been employed in the synthesis of 1-substituted tetrahydroisoquinolines (R)-13 including the alkaloid (-)-homolaudanosine ((R)-13d) as outlined below. By hydrogenation in acetic acid/1% trifluoroacetic acid using Pd on carbon (10% Pd) as catalyst the amides (S)-11/(R)-12 a-c were obtained. Said diastereomers (S)-11/(R)-12 proved to be separable on silica gel. The ratio (S)-11/(R)-12 was found to be almost the same as the (S)-9/(R)-10 ratio (see Table 1.) except for the compounds with a p-chlorophenyl substituent (Table 1. entry 5). This might be due to a difference in the rate of a side reaction which occurred during hydrogenation. Beside the carbonyl oxygen also the chlorine substituent had been removed to some extent (up to 36%).

The yields of the major diastereomers (R)-12 in pure form obtainded after flash chromatography are also set forth in Table 1. The next step involved the cleavage of the amide bond and was first attempted by means of LiOH in dioxane/H_2O (3/1, sealed tube, ~150°C), but without any noticeable success.

Finally we found that amides (R)-12a - (R)-12c can be cleaved by treatment with $LiAlH_4$ in THF (2.5 - 5.0 mol.-eq., 2-3 h, 20°C). The pure amines (R)-13a - (R)-13c were thus obtained in fairly good yields (Table 2) after flash chromatography

(SiO_2, Et_2O/NEt_3=95/5). The lower yield for (R)-13b is due to the fact that for convenience a mixture of (R)-12b and (R)-12a (obtained from hydrogenolysis, vide supra) had been employed as starting material.



(R)-13

Table 2.

(R)-13

	R^1	R^2	R^3	Yield [%]	$[\alpha]_{578}$
a	H	H	H	64.7	+25.5°
b	Cl	H	H	16.1[a)]	+12.4°
c	OCH_3	OCH_3	H	77.0	+15.1°
d	OCH_3	OCH_3	CH_3	64.3	-13.5°

a) Based on starting material contaminated with 36% (R)-12a.

The R stereochemistry of (R)-13b has been established by comparing the optical rotation ($[\alpha]_{578}$ = +12.4°, $[\alpha]_{546}$ = +11.5°; c= 1.05; CH_3OH) with reported literature values[9] ($[\alpha]_D$ = +15°; CH_3OH). The R configuration of (R)-13a could be deduced from the product distribution that was observed after hydrogenation of (S)-9b/(R)-10b. Thereby in addition to (S)-11b/(R)-12b a mixture of (S)-11a/(R)-12a was formed (vide supra) wherein the predominant isomer was the same as in the product obtained along the direct route from (S)-9a/(R)-10a (verified by HPLC).

The final step in the synthesis of (R)-homolaudanosine ((R)-13d) was the methylation of (R)-13c (CH_2O, 2.5 eq. $NaCNBH_3$) which afforded (R)-13d in 64.3% yield. The optical rotation of the obtained product ($[\alpha]_{578}$ = -13.5°, c= 0.89, EtOH) compared to that of the natural enantiomer[10] ((S)-13d: $[\alpha]_D$ = + 11°, c= 0.21, EtOH) indicates that the synthesized compounds and its precursors belong to the (R)-series. In order to verify the optical purity of the amines (R)-13 a sample of (R)-13a was treated with (-)-camphanic acid chloride. HPLC revealed (R)-12a as the prevailing compound, accompanied by trace amounts (< 0.4%) of a side product (possibly (S)-11a). Therefore the optical purity (ee) of (R)-13a - (R)-13d should at least be higher than 99%.

In conclusion, it has been shown that the chiral acyliminium ion (6) can be obtained by a simple hydride abstraction reaction. Subsequent trapping reactions

proceed with stereoselective bond formation and the resulting products are useful intermediates in the synthesis of 1-substituted tetrahydroisoquinolines of high enantiomeric purity.

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