Stereoselective Synthesis of (*S*)-3,4-Methylenedioxyamphetamines from (*R*)-Cyanohydrins**

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Abstract: A stereoselective synthesis of (*S*)-3,4-methylenedioxyamphetamines (*S*)-**7**, which are highly interesting as psychoactive compounds, is described. Starting from readily available (*R*)-cyanohydrins (*R*)-**2** the 2-amino-1-aryl alcohols (1*R*,2*S*)-**4** were obtained with high diastereoselectivity by addition of Grignard reagents to the *O*-protected cyanohydrins (*R*)-**3**, transimination of the addition products **A** with primary amines, and hydrogenation of the imino intermediates **B** with $NaBH_4$. For the hydrogenation of the benzylic hydroxyl group in the 1,2-amino alcohols (1*R*,2*S*)-**4** a new, very efficient method was developed. The optically pure amphetamines (*S*)-**7** were obtained under very mild conditions by catalytic hydrogenation of the oxazolidinones (4*S*,5*R*)-**6**, which were readily available by phosgenation of the amino alcohols (1*R*,2*S*)-**4**.

Introduction

3,4-Methylenedioxy-substituted amphetamines have received great attention in the last years as important representatives of the so-called "designer drugs".[1] 3,4-Methylenedioxymethamphetamine (MDMA), for example, commonly known as "Ecstasy", has been reported to produce both stimulant and hallucinogen-like effects in humans.[2] Whereas 2,5-dimethoxyamphetamine (DMA) is a much stronger hallucinogen than mescaline, the corresponding 3,4-methylenedioxyamphetamines are considerably less potent.[3] By introduction of *N*-alkyl substituents or by changing from 1,2-ethanolamines to 1,2-propanolamines or 1,2-butanolamines, the hallucinogenic effect almost disappears.[2b, 4, 5] 3,4-Methylenedioxyamphetamines like MDMA possess antidepressive and anxiolytic properties. Reportedly they are able to evoke a well-controllable emotional experience with relaxation, a drop in fear responses, peaceful feelings, and increased empathy.[2, 5] Since these positive changes of behavior occur mostly without distortion of sensory perception and thought and without marked stimulation, these compounds could be of great medical usefulness as adjuncts in insight-oriented psychotherapy.[6]

Investigations of differences in the biological effects of the two enantiomers of MDMA have shown that the (*S*, +) enantiomer is more potent as a "positive" stimulant, whereas the (*R*, −) enantiomer is a markedly stronger hallucinogen. For psychotherapeutical applications of this new class of psychoactive compounds, therefore, comprehensive, more general investigations into the biological activity of the optically pure enantiomers of 3,4-methylenedioxyamphetamines[7] and their metabolites[8] are necessary.

The preparation of optically pure enantiomers of 3,4-methylenedioxyamphetamines has already been published by Nichols et al.:[7a] ketones are allowed to react with optically active 1-phenylethylamine to give the corresponding imino compounds, which are diastereoselectively hydrogenated to amines in situ with Raney nickel; to complete the reaction the phenethyl group at the amino function must be removed by catalytic hydrogenation.[7a] A disadvantage of this procedure, in most cases, is the costly preparation of the starting ketones.

The hydrogenation of 2-amino-1-aryl alcohols is an alternative approach for the synthesis of optically pure amphetamines, as demonstrated by the preparation of (*S*)-methamphetamine from (1*R*,2*S*)-ephedrine.[9] Whereas the hydrogenation of the hydroxyl group itself is difficult and gives only low yields, the corresponding 1-chloro-1-phenyl-2-aminopropane, prepared from the amino alcohol with $SOCl_2$, can be hydrogenated more readily.[10] This route for the preparation of (*S*)-amphetamines was mainly limited to (1*R*,2*S*)-ephedrine as starting compound since other suitable 2-amino-1-aryl alcohols were accessible only as racemates.

Since (1*R*,2*S*)-2-amino-1-aryl alcohols as pure stereoisomers became readily available from (*R*)-cyanohydrins in the last few years,[11–13] we have comprehensively investigated the stereoselective synthesis of 3,4-dioxy substituted (*S*)-amphetamines

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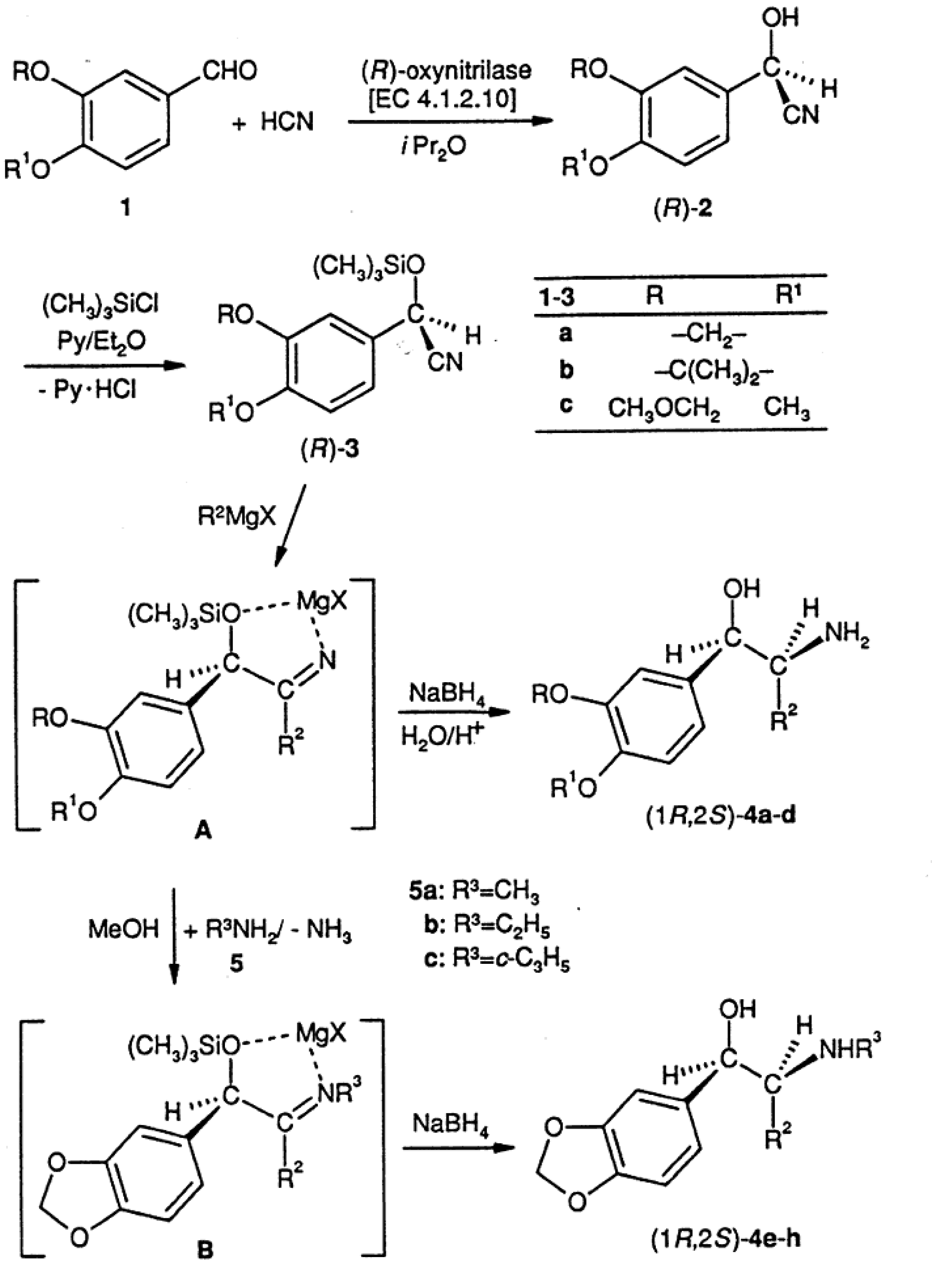
[+] This work is part of the dissertation of Jürgen Jäger, Universität Stuttgart, **1996**.

[**] Enzyme-Catalyzed Reactions, Part 29; Part 28, see ref. [14].

from the corresponding (1*R*,2*S*)-amino alcohols. We were especially interested in the preparation of the 3,4-methylenedioxy compounds for psychotherapeutical applications.

Results and Discussion

Synthesis of (1*R*,2*S*)-2-amino-1-aryl alcohols (1*R*,2*S*)-4: The reaction sequence we have applied for the synthesis of the (1*R*,2*S*)-2-amino alcohols, which are the starting compounds for the preparation of the desired (*S*)-amphetamines, is shown in Scheme 1.



1-3	R	R¹
a	$-CH_2-$	
b	$-C(CH_3)_2-$	
c	CH_3OCH_2	CH_3

4	R	R¹	R²	4	R²	R³
a	$-CH_2-$		CH_3	**e**	CH_3	CH_3
b	$-CH_2-$		C_2H_5	**f**	CH_3	C_2H_5
c	$-C(CH_3)_2-$		CH_3	**g**	CH_3	*c*-C_3H_5
d	CH_3OCH_2	CH_3	CH_3	**h**	C_2H_5	CH_3

Scheme 1. Enzyme-catalyzed addition of HCN to aldehydes **1** to give (*R*)-cyanohydrins **2** and subsequent preparation of (1*R*,2*S*)-2-amino-1-aryl alcohols **4a–d** and (1*R*,2*S*)-2-alkylamino-1-aryl alcohols **4e–h**.

In an enzyme-catalyzed addition of HCN to the *O*-protected 3,4-dihydroxybenzaldehydes **1**, the corresponding cyanohydrins (*R*)-**2** were obtained with high optical purity.[11a, 13c, 14] Addition of Grignard compounds to the nitrile group of the *O*-silyl-protected cyanohydrins (*R*)-**3** led to the imino intermediates **A**. Direct hydrogenation of **A** with $NaBH_4$ and acidic workup yielded the *N*-unsubstituted 2-amino alcohols (1*R*,2*S*)-**4a–d**.[12] The 2-alkylamino-1-aryl alcohols (1*R*,2*S*)-**4e–h** were accessible by treatment of the imino intermediates **A** with methanol, transimination with a primary amine **5**, and subsequent hydrogenation of the *N*-alkylimino compounds **B** with $NaBH_4$.[13]

For the synthesis of the pharmacologically interesting amphetamines methylenedioxyamphetamine (MDA, "Love Drug"), methylenedioxymethamphetamine (MDMA, "Ecstasy"), and methylenedioxyethylamphetamine (MDE, "Eve"), we used the hydroxy-protected 3,4-dihydroxybenzaldehydes piperonal (**1a**), 2,2-dimethyl-5-formyl-1,3-benzodioxol (**1b**), and 3-methoxymethylenoxy-4-methoxybenzaldehyde (**1c**)[14] as substrates in the (*R*)-oxynitrilase-mediated cyanohydrin formation (Scheme 1). As previously reported, the (*R*)-cyanohydrins (*R*)-**2a,b** are available with *ee* values of 93–99% and good chemical yields;[11a, 13c] however, (*R*)-**2c** can only be obtained with 81% *ee*.[14] According to the published procedure,[12b] the trimethylsilyl protecting group was introduced in cyanohydrins (*R*)-**2a–c** yielding the *O*-silylated cyanohydrins (*R*)-**3a–c** with 39–60% yield based on the respective aldehydes **1a–c**. The results of the preparation of the (1*R*,2*S*)-2-amino alcohols (1*R*,2*S*)-**4** from (*R*)-**3** (Scheme 1) are summarized in Table 1.

Table 1. Synthesis of (1*R*,2*S*)-2-amino-1-aryl alcohols (1*R*,2*S*)-**4** from *O*-silylated (*R*)-cyanohydrins (*R*)-**3**.

(*R*)-3	R^2MgX	5	(1*R*,2*S*)-4	Yield/% [a]	*de*/% [b]	$[\alpha]_D^{20}$ (*c* in MeOH)	M.p./°C
a	CH_3MgI	–	**a**	51	95	−32.5 (1.40)	212
a	C_2H_5MgBr	–	**b**	45	90	−29.0 (1.00)	201
b	CH_3MgI	–	**c**	38	>95	−15.2 (1.10)	192 [d]
c	CH_3MgI	–	**d**	13 [c]	90	−10.0 (0.70)	204 [d]
a	CH_3MgI	**a**	**e**	47	77	−41.6 (0.80)	223 [d]
a	CH_3MgI	**b**	**f**	47	>95	−28.0 (1.00)	222
a	CH_3MgI	**c**	**g**	57	>98	−26.6 (0.80)	194
a	C_2H_5MgBr	**a**	**h**	44	92	−31.6 (1.20)	194

[a] After crystallization as the hydrochloride. [b] Determined from crude product by ^1H NMR spectroscopy. [c] Isolated as free amino alcohol after chromatography. [d] Decomposition.

As can be seen from Table 1, the (1*R*,2*S*)-amino alcohols **4** can be isolated with a diastereomeric excess of greater than 90% *de*, with the exception of (1*R*,2*S*)-**4e** (only 77% *de*).

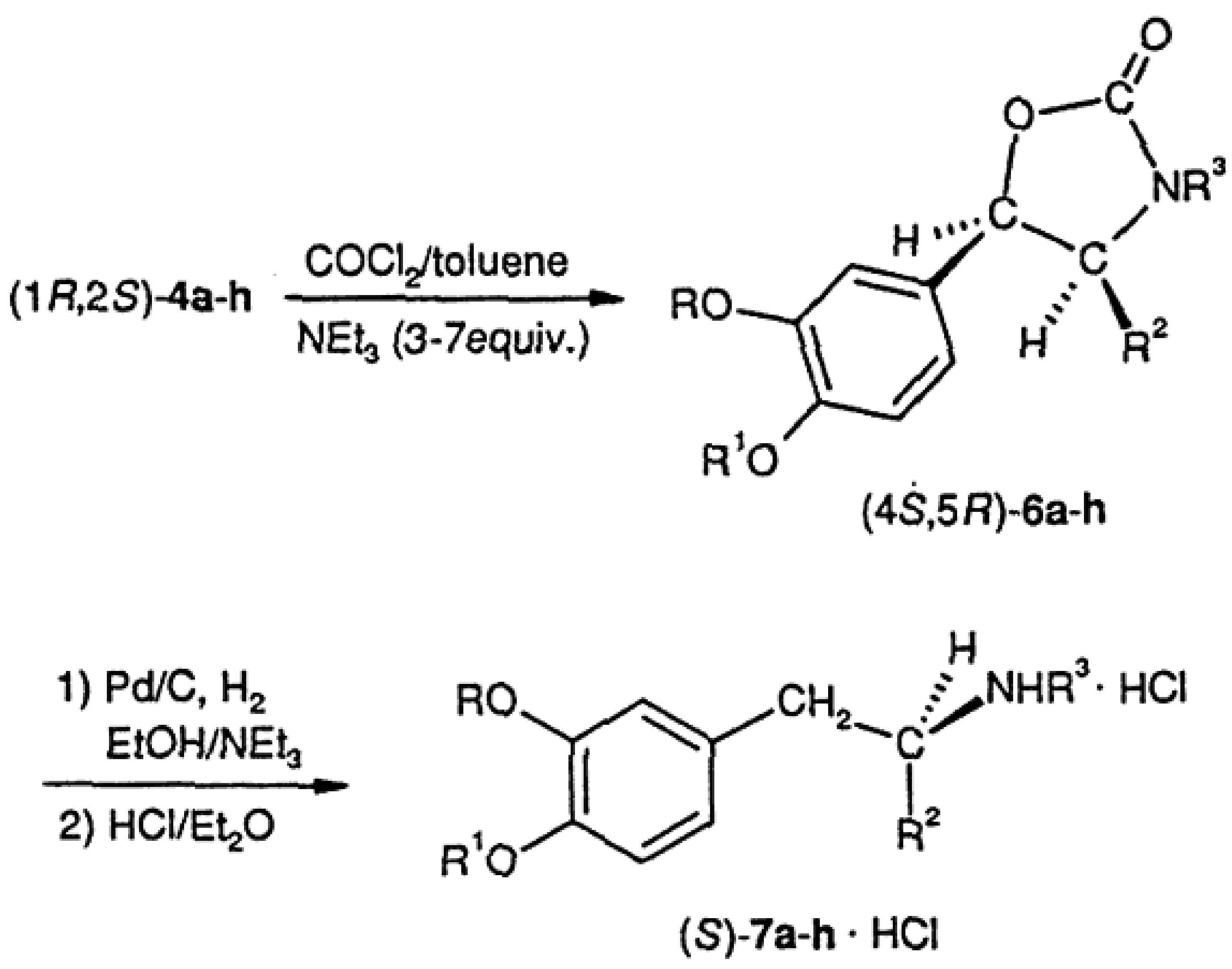
Transformation of (1*R*,2*S*)-4 into (*S*)-amphetamines (*S*)-7 by catalytic hydrogenation of oxazolidinones (4*S*,5*R*)-6: It is known that the catalytic hydrogenation of benzylic hydroxyl groups can be facilitated by improving their ability to act as leaving groups, for example, by acetylation.[15] The addition of triethylamine to the reaction mixture causes a further acceleration of the hydrogenation of acetylated benzyl alcohols.[16] The hydrogenation of (1*R*,2*S*)-ephedrine to (*S*)-methamphetamine in acetic acid/perchloric acid at 80–90 °C described by Rosenmund and Karg[9] is therefore assumed to proceed via the *O*-acetylated compound. Since only relatively low yields of amphetamine are obtained with the amino alcohols themselves, despite the drastic reaction conditions,[9] we decided to investigate the hydrogenation of the *O*-acetyl-2-amino alcohols.

A selective *O*-acetylation of 1,2-amino alcohols is not possible without using protecting groups, since even monoacetylated ephedrine, for example, undergoes a fast N↔O shift of the acetyl group.[17] As model reaction we therefore first studied the catalytic hydrogenation of *O*,*N*-diacetylnorephedrine in ethanol with addition of triethylamine[16] at room temperature. Hydrogen uptake was complete after only 3 hours, and we were able to isolate the corresponding *N*-acetylamphetamine in 90% yield. The removal of the *N*-acetyl group, however, was difficult, and we did not succeed in achieving complete deprotection with standard methods.

The concept that we applied to avoid these difficulties was the introduction of an "intramolecular" urethane protecting group. The 1,3-oxazolidin-2-ones **6**, which should be readily accessible from the 1,2-amino alcohols **4** and phosgene[18a] or other carbonic acid derivatives,[18b–e] can be viewed as cyclic urethanes. The OH group incorporated in the oxazolidinone ring should be sufficiently activated for hydrogenation, and the carbamic acid formed by hydrogenation should decarboxylate readily.

Based on the procedure described by Fodor et al.,[18a] the 1,3-oxazolidin-2-ones (4*S*,5*R*)-**6** were prepared by reaction of 1,2-amino alcohols (1*R*,2*S*)-**4** in dichloromethane with a solution of phosgene in toluene and triethylamine (3–7-fold excess relative to **4**) (Scheme 2, Table 2). In order to achieve higher yields of oxazolidinones **6** the free amino alcohols **4** were generally used instead of the corresponding hydrochlorides.

Table 2 shows that the 1,3-oxazolidin-2-ones (4*S*,5*R*)-**6** were isolated with excellent yields. The oxazolidinones (4*S*,5*R*)-**6a**, **b**,**e**–**g** were purified by recrystallization from dichloromethane/petroleum ether, while compounds (4*S*,5*R*)-**6c**,**d**,**h**, which were obtained as oils, were purified by chromatography on silica gel. In the case of (1*R*,2*S*)-**4d**, the reaction proceeded slowly and was accompanied by formation of by-products. Moreover, the product (4*S*,5*R*)-**6d** partly decomposed during chromatography. The low specific rotation (Table 2) indicated partial racemization.



6, 7	R	R¹	R²	R³	**6, 7**	R	R¹	R²	R³
a	$-CH_2-$		CH_3	H	**e**	$-CH_2-$		CH_3	CH_3
b	$-CH_2-$		C_2H_5	H	**f**	$-CH_2-$		CH_3	C_2H_5
c	$-C(CH_3)_2-$		CH_3	H	**g**	$-CH_2-$		CH_3	$c\text{-}C_3H_5$
d	CH_3OCH_2	CH_3	CH_3	H	**h**	$-CH_2-$		C_2H_5	CH_3

Scheme 2. Preparation of (*S*)-amphetamines **7** via the corresponding 1,3-oxazolidin-2-ones (4*S*,5*R*)-**6**.

Table 2. Synthesis of (4*S*,5*R*)-oxazolidinones (4*S*,5*R*)-**6** from (1*R*,2*S*)-2-amino alcohols **4** with phosgene in toluene in the presence of triethylamine (3–7 equiv).

(1*R*,2*S*)-4	*t*/min	(4*S*,5*R*)-**6**	Yield/%	$[\alpha]_D^{20}$ (*c* in CH_2Cl_2)	M.p./°C
a	30	**a**	97	−90.0 (1.30)	105–106
b	60	**b**	90	−91.5 (1.00)	133–134
c	30	**c**	88	−77.5 (1.40)	–
d	120	**d**	40 [a]	−2.4 (1.00)	–
e	30	**e**	91	−60.4 (1.00)	133
f	30	**f**	93	−51.0 (1.10)	87.5
g	30	**g**	96	−67.8 (1.10)	123
h	60	**h**	81	−13.9 (1.25)	–

[a] Contaminated despite chromatography twice.

A method for determination of diastereomeric excess could not be developed so far. In all cases, however, ^1H NMR spectra show only one diastereomer. The specific rotation of (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidin-2-one, prepared analogously from (1*S*,2*R*)-(+)-norephedrine, agreed with published data;[18a, 19] this confirms that the reactions proceed without racemization.

The hydrogenation of 1,3-oxazolidin-2-ones has not yet been reported in the literature. We have now performed the catalytic hydrogenation of the oxazolidinones (4*S*,5*R*)-**6** to the (*S*)-amphetamines (*S*)-**7** under the reaction conditions described above for the hydrogenation of diacetylnorephedrine (Scheme 2, Table 3). The reaction was followed by gas chromatography. The (*S*)-amphetamines **7** were converted into their hydrochlorides for characterization.

Table 3. (*S*)-Amphetamines (*S*)-**7** from (4*S*,5*R*)-oxazolidinones **6** by catalytic hydrogenation.

(4*S*,5*R*)-**6**	*t*/h	(*S*)-7·HCl	Yield/%	*ee*/% [a]	$[\alpha]_D^{20}$ (*c* in H_2O)	M.p./°C
a	3	**a**	89	>95	+26.6 (1.40)	198
b	3	**b**	92	98	+35.6 (1.10)	165 [f]
c	6	**c**	98 [b]	n.d.	+17.0 (0.80) [c]	165 [f]
d	5	**d** [d]	90 [b]	30	−9.3 (1.00) [c]	150 [f]
e	2	**e**	96	>99	+17.9 (1.00)	187
f	5	**f**	93	>98	+14.3 (2.00)	204
g	4	**g**	47 [e]	98	+17.6 (1.00)	166
h	5	**h**	89	>95	+26.1 (1.00)	181

[a] Determined by HPLC on chiral phases; assignment by comparison with the corresponding racemic amphetamines **7** as reference. [b] Yield based on free amine. [c] In methanol. [d] Removal of the methoxymethyl protecting group during conversion to the hydrochloride. [e] Partial cleavage of the cyclopropane ring to 1-(1,3-benzodioxol-5-yl)-2-propylaminopropane. [f] Decomposition.

The oxazolidinones (4*S*,5*R*)-**6** were almost quantitatively hydrogenated to amphetamines (*S*)-**7**. Minor loss of yield was caused by conversion into the hydrochlorides (*S*)-**7**·HCl. The relatively low yield obtained for the hydrogenation of **6g** can be attributed to a partial cleavage of the cyclopropane ring to give 1-(1,3-benzodioxol-5-yl)-2-propylaminopropane, which could be separated from (*S*)-**7g** by chromatography. In the case of (*S*)-**7d** the methoxymethyl protecting group was removed under the conditions of the hydrochloride formation.

The catalytic hydrogenation of 2-amino-1-aryl alcohols to (*S*)-amphetamines via 1,3-oxazolidin-2-ones represents a decisive improvement in comparison with procedures described so far.[9, 10] Even without pressure and at room temperature the yields are practically quantitative.

Conclusion

The described stereoselective synthesis of (*S*)-3,4-methylenedioxyamphetamines from (*R*)-cyanohydrins opens not only the possibility for a broad structural variation of an important class of biologically active compounds, but also for the preparation of their optically active metabolites. Only a precise knowledge of all the biological effects of the pure stereoisomers of these important but controversial psychoactive compounds will allow their risks or medical usefulness to be assessed and predicted.

Experimental Section

Materials and methods: Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250F (250 MHz) with TMS as internal standard. Preparative column chromatography was carried out on columns packed with silica gel S (Riedel-de Haen, grain size 0.032–0.063 mm). Specific rotations were measured on a Perkin-Elmer polarimeter 241 LC. Reactions were followed by GC using Hewlett-Packard 5700A and 5710A with FID, nitrogen 30 mL min^{-1}, glass column (2.3 m × 2 mm), phases OV7, 17, 101, 225 (3–5%) on chromosorb W. Avicel cellulose and (+)-norephedrine were purchased from Merck, piperonal (**1a**) from Fluka, and Pd/C (10%) from Degussa AG. All solvents were dried and distilled. Reactions with organometallic compounds were carried out under argon or nitrogen atmosphere in dried glassware. The following aldehydes were prepared according to known procedures: 2,2-dimethyl-5-formyl-1,3-benzodioxol (**1b**) (from 5-bromo-2,2-dimethyl-1,3-benzodioxol[20]),[21] 3-methoxymethylenoxy-4-methoxybenzaldehyde (**1c**).[14]

Silylation of (*R*)-cyanohydrins (*R*)-2 to (*R*)-3:[12b] At 0 °C pyridine (1 equivalent) was added to a solution of cyanohydrin (*R*)-**2**[11a, 13c, 14] in dry diethyl ether followed by the dropwise addition of trimethylchlorosilane (1 equivalent) and the reaction mixture stirred for 5 h at room temperature. Precipitated pyridinium hydrochloride was filtered off and washed with dry diethyl ether. The combined filtrates were concentrated and the residue distilled through a Vigreux column.

(*R*)-2-(1,3-Benzodioxol-5-yl)-2-trimethylsilyloxyacetonitrile (3a): ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.22 (s, 9H, (CH$_3$)$_3$), 5.38 (s, 1H, CH), 6.00 (s, 2H, OCH$_2$O), 6.81 (d, *J* = 7.9 Hz, 1H, ArH), 6.92 (dd, *J* = 7.9, 1.7 Hz, 1H, ArH), 6.96 (d, *J* = 1.7 Hz, 1H, ArH); $C_{12}H_{15}NO_3Si$ (249.3): calcd C 57.80, H 6.06, N 5.62; found C 58.04, H 6.11, N 5.54.

(*R*)-2-(2,2-Dimethyl-1,3-benzodioxol-5-yl)-2-trimethylsilyloxyacetonitrile (3b): ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.22 (s, 9H, (CH$_3$)$_3$), 1.68 (s, 6H, C(CH$_3$)$_2$), 5.36 (s, 1H, CH), 6.71 (d, *J* = 8.4 Hz, 1H, ArH), 6.84–6.87 (m, 2H, ArH); $C_{14}H_{19}NO_3Si$ (277.4): calcd C 60.61, H 6.90, N 5.05; found C 60.73, H 6.85, N 4.79.

(*R*)-2-(3-Methoxymethylenoxy-4-methoxyphenyl)-2-trimethylsilyloxyacetonitrile (3c): ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.23 (s, 9H, (CH$_3$)$_3$), 3.52 (s, 3H, CH$_3$O), 3.92 (s, 3H, *CH*$_3$OCH$_2$), 5.25 (s, 2H, CH$_3$O*CH*$_2$), 5.43 (s, 1H, CH), 6.95 (dd, *J* = 8.3, 2.1 Hz, 1H, ArH), 7.03 (d, *J* = 2.1 Hz, 1H, ArH), 7.16 (d, *J* = 8.3 Hz, 1H, ArH); $C_{14}H_{21}NO_4Si$ (295.4): calcd C 56.92, H 7.17, N 4.74; found C 56.78, H 7.09, N 4.59.

(1*R*,2*S*)-2-Amino-1-aryl alcohols (1*R*,2*S*)-4a–d: According to the known procedure,[12b] purification as described below for **4e–h**.

General procedure for the synthesis of (1*R*,2*S*)-2-alkylamino-1-aryl alcohols (1*R*,2*S*)-4e–h: At 0 °C a solution of (*R*)-**3** (4—48 mmol) in diethyl ether was added dropwise to a solution of the Grignard reagent, prepared from Mg and alkyl halide in diethyl ether,[12b] and the reaction mixture stirred for 3–4 h at room temperature. After cooling to 0 °C a solution of amine **5** (2–12 fold excess of **3**) in methanol (3–20 mL) was added dropwise. The reaction mixture was stirred for 1–1.5 h at room temperature and cooled to −60 °C, and NaBH$_4$ added in portions. The reaction mixture was allowed to warm up to room temperature within 16 h, hydrolyzed with 0.1 N HCl, the aqueous phase set to pH 2, and the organic phase separated. The aqueous phase was adjusted to pH 9–10 with NaOH solution and extracted with diethyl ether or ethyl acetate. The combined extracts were dried (MgSO$_4$), concentrated, and the residue chromatographed on silica gel with THF/NH$_3$ sat. ethanol (12:1) or ethyl acetate/NH$_3$ sat. methanol (30:1). For purification the product either was crystallized from diethyl ether/petroleum ether or precipitated as hydrochloride with ethereal HCl solution and recrystallized from ethanol/diethyl ether.

4b: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.90–1.00 (m, 3H, CH$_2$*CH*$_3$), 1.00–1.20 (m, 1H, *CH*$_2$CH$_3$), 1.30–1.60 (m, 1H, *CH*$_2$CH$_3$), 1.80 (brs, 3H, NH$_2$, OH), 2.85 (mc, 1H, 2-CH), 4.47 (d, *J* = 5.1 Hz, 1H, 1-CH), 5.95 (s, 2H, OCH$_2$O), 6.77 (d, *J* = 0.8 Hz, 2H, ArH), 6.85 (s, 1H, ArH); $C_{11}H_{17}NO_3\cdot HCl$ (245.7): calcd C 53.77, H 6.56, N 5.70, Cl 14.43; found C 53.72, H 6.44, N 5.72, Cl 14.51.

4d: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.00 (d, *J* = 6.5 Hz, 3H, CH$_3$), 3.16 (dq, *J* = 5.0, 6.5 Hz, 1H, 2-CH), 3.52, 3.53 (each s, 3H, CH$_3$O), 4.44 (d, *J* = 5.0 Hz, 1H, 1-CH), 5.22 (s, 2H, CH$_3$O*CH*$_2$), 6.80 (dd, *J* = 1.7, 8.2 Hz, 1H, ArH), 6.90 (d, *J* = 1.7 Hz, 1H, ArH), 7.10 (d, *J* = 8.2 Hz, 1H, ArH).

4e·HCl: ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 0.94 (d, *J* = 6.7 Hz, 3H, CH$_3$), 2.59 (s, 3H, NCH$_3$), 3.28 (brs, 1H, 2-CH), 5.07–5.09 (m, 1H, 1-CH), 6.01 (s, 2H, OCH$_2$O), 6.12 (d, *J* = 4.4 Hz, 1H, OH), 6.85–6.95 (m, 3H, ArH), 8.98 (bd, *J* = 22.0 Hz, 2H, NH$_2^+$); $C_{11}H_{15}NO_3\cdot HCl$ (245.7): calcd C 53.77, H 6.56, N 5.70, Cl 14.43; found C 53.98, H 6.55, N 5.72, Cl 14.33.

4f: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.85 (d, *J* = 6.5 Hz, 3H, CH$_3$), 1.14 (t, *J* = 7.1 Hz, 3H, CH$_2$*CH*$_3$), 2.60–2.85 (m, 4H, N*HCH*$_2$CH$_3$, OH), 2.90 (dq, *J* = 4.0, 6.5 Hz, 1H, 2-CH), 4.70 (d, *J* = 4.0 Hz, 1H, 1-CH), 5.94 (s, 2H, OCH$_2$O), 6.77 (d, *J* = 1.0 Hz, 2H, ArH), 6.85 (d, *J* = 0.5 Hz, 1H, ArH); $C_{12}H_{17}NO_3\cdot HCl$ (259.7): calcd C 55.49, H 6.99, N 5.39, Cl 13.65; found C 55.30, H 7.06, N 5.58, Cl 13.48.

4g: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.33–0.43 (m, 2H, CH$_2$), 0.44–0.54 (m, 2H, CH$_2$), 0.86 (d, *J* = 6.5 Hz, 3H, CH$_3$), 2.16 (mc, 1H, NHC*H*), 3.00 (dq, *J* = 4.0, 6.5 Hz, 1H, 2-CH), 4.73 (d, *J* = 4.0 Hz, 1H, 1-CH), 5.94 (s, 2H, OCH$_2$O), 6.76 (d, *J* = 0.7 Hz, 2H, ArH), 6.84 (s, 1H, ArH); $C_{13}H_{17}NO_3\cdot HCl$ (271.7): calcd C 57.46, H 6.68, N 5.16, Cl 13.04; found C 57.49, H 6.66, N 5.03, Cl 13.16.

4h·HCl: ^{1}H NMR (250 MHz, [D$_6$]DMSO): δ = 0.84 (t, *J* = 7.4 Hz, 3H, CH$_2$*CH*$_3$), 1.11–1.38 (m, 2H, *CH*$_2$CH$_3$), 2.40–2.51 (m, 1H, 2-CH), 4.72 (d, *J* = 4.2 Hz, 1H, 1-CH), 5.94 (s, 2H, OCH$_2$O), 6.77 (d, *J* = 1.0 Hz, 2H, ArH), 6.85 (s, 1H, ArH); $C_{12}H_{17}NO_3\cdot HCl$ (259.7): calcd C 55.49, H 6.99, N 5.39, Cl 13.65; found C 55.28, H 7.00, N 5.39, Cl 13.61.

General procedure for the synthesis of (4*S*,5*R*)-1,3-oxazolidin-2-ones (4*S*,5*R*)-6: To an ice-cold solution of (1*R*,2*S*)-**4** in dichloromethane (ca. 50 mM) and triethylamine (3–7 fold excess of **4**) a 2 M solution of phosgene in toluene[18a] (1.1–1.5 equiv based on **4**) was added dropwise, and the reaction mixture stirred at room temperature for the time given in Table 2. After hydrolysis with NaOH solution (5%) the organic phase was washed with NaOH solution (5%) and water, dried (MgSO$_4$), and the solvent removed. The residue was crystallized from dichloromethane/petroleum ether or chromatographed on silica gel with ethyl acetate/petroleum ether (7:3).

6a: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.86 (d, *J* = 6.5 Hz, 3H, CH$_3$), 4.15 (dq, *J* = 6.5, 8.0 Hz, 1H, 4-CH), 5.62 (d, *J* = 8.0 Hz, 1H, 5-CH), 5.98 (s, 2H, OCH$_2$O), 6.10 (brs, 1H, NH), 6.72–6.83 (m, 3H, ArH); $C_{11}H_{11}NO_4$ (221.2): calcd C 59.72, H 5.01, N 6.33; found C 59.59, H 5.04, N 6.20.

6b: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.82 (t, *J* = 7.3 Hz, 3H, CH$_2$*CH*$_3$), 1.07–1.17 (m, 2H, *CH*$_2$CH$_3$), 3.91 (dt, *J* = 5.4, 8.1 Hz, 1H, 4-CH), 5.62 (d, *J* = 8.1 Hz, 1H, 5-CH), 5.99 (s, 2H, OCH$_2$O), 6.61 (brs, 1H, NH), 6.73–6.82 (m, 3H, ArH); $C_{12}H_{13}NO_4$ (235.2): calcd C 61.27, H 5.57, N 5.96; found C 61.27, H 5.58, N 5.89.

6c: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.87 (d, *J* = 6.6 Hz, 3H, CH$_3$), 1.67 (s, 3H, CH$_3$), 1.68 (s, 3H, CH$_3$), 4.15 (dq, *J* = 6.6, 8.0 Hz, 1H, 4-CH), 5.60 (d, *J* = 8.0 Hz, 1H, 5-CH), 6.50 (s, 1H, NH), 6.67–6.76 (m, 3H, ArH); $C_{13}H_{15}NO_4$ (249.3): calcd C 62.64, H 6.06, N 5.62; found C 62.86, H 6.12, N 5.54.

6d: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.85 (d, *J* = 6.5 Hz, 3H, CH$_3$), 3.52 (s, 3H, CH$_3$O), 3.90 (s, 3H, *CH*$_3$OCH$_2$), 4.15 (dq, *J* = 6.5, 7.9 Hz, 1H, 4-CH), 5.24 (s, 2H, CH$_3$O*CH*$_2$), 5.67 (d, *J* = 7.9 Hz, 1H, 5-CH), 5.86 (s, 1H, NH), 6.78 (dd, *J* = 1.9, 8.2 Hz, 1H, ArH), 6.79 (d, *J* = 1.9 Hz, 1H, ArH), 7.16 (d, *J* = 8.2 Hz, 1H, ArH).

6e: ^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.83 (d, *J* = 6.6 Hz, 3H, CH$_3$), 2.87 (s, 3H, NCH$_3$), 3.97 (dq, *J* = 6.6, 8.2 Hz, 1H, 4-CH), 5.49 (d, *J* = 8.2 Hz, 1H, 5-CH), 5.98 (s, 2H, OCH$_2$O), 6.70–6.82 (m, 3H, ArH); $C_{12}H_{13}NO_4$ (235.2): calcd C 61.27, H 5.57, N 5.96; found C 61.22, H 5.71, N 6.00.

6f: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 0.81$ (d, $J = 6.6$ Hz, 3H, $\mathrm{CH_3}$), 1.19 (t, $J = 7.2$ Hz, 3H, $\mathrm{CH_2C}H_3$), 3.58 (dq, $J = 7.2$, 14.2 Hz, 1H, $CH_2\mathrm{CH_3}$), 3.70 (dq, 1H, $CH_2\mathrm{CH_3}$), 4.08 (dq, $J = 6.6$, 8.2 Hz, 1H, 4-CH), 5.47 (d, $J = 8.2$ Hz, 1H, 5-CH), 5.98 (s, 2H, $\mathrm{OCH_2O}$), 6.70–6.82 (m, 3H, ArH); $\mathrm{C_{13}H_{15}NO_4}$ (249.3): calcd C 62.64, H 6.06, N 5.62; found C 62.80, H 5.87, N 5.70.

6g: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 0.56$–0.77 (m, 2H, $\mathrm{CH_2}$), 0.84–1.02 (m, 2H, $\mathrm{CH_2}$), 0.89 (d, $J = 6.6$ Hz, 3H, $\mathrm{CH_3}$), 2.40–2.50 (mc, 1H, NCH), 3.91 (dq, $J = 6.6$, 7.7 Hz, 1H, 4-CH), 5.41 (d, $J = 7.7$ Hz, 1H, 5-CH), 5.94 (s, 2H, $\mathrm{OCH_2O}$), 6.76 (d, $J = 0.7$ Hz, 2H, ArH), 6.83 (s, 1H, ArH); $\mathrm{C_{14}H_{15}NO_4}$ (261.3): calcd C 64.35, H 5.79, N 5.36; found C 64.24, H 5.90, N 5.51.

6h: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 0.65$ (t, $J = 7.4$ Hz, 3H, $\mathrm{CH_2C}H_3$), 1.28–1.57 (m, 2H, $CH_2\mathrm{CH_3}$), 2.91 (s, 3H, $\mathrm{NCH_3}$), 3.77 (dt, $J = 4.2$, 8.1 Hz, 1H, 4-CH), 5.48 (d, $J = 8.1$ Hz, 1H, 5-CH), 5.98 (s, 2H, $\mathrm{OCH_2O}$), 6.75–6.82 (m, 3H, ArH); $\mathrm{C_{13}H_{15}NO_4}$ (249.3): calcd C 62.64, H 6.06, N 5.62; found C 62.67, H 6.33, N 5.34.

General procedure for the catalytic hydrogenation of oxazolidinones (4*S*,5*R*)-6 to (*S*)-amphetamines (*S*)-7: A vigorously stirred solution of (4*S*,5*R*)-**6** (0.4–14 mmol) in ethanol containing 5% triethylamine was hydrogenated at room temperature with Pd/C (ca. 10 mol%) as catalyst for the time given in Table 3 (GC control). The catalyst was filtered off and the solvent removed. After removal of $\mathrm{NEt_3}$ in high vacuo the residue was dissolved in diethyl ether, and amphetamine hydrochlorides precipitated by addition of ethereal HCl solution.

7a: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 1.11$ (d, $J = 6.3$ Hz, 3H, $\mathrm{CH_3}$), 1.63 (brs, 2H, $\mathrm{NH_2}$), 2.44 (ABX system, $J_{AB} = 13.4$, $J_{AX} = 8.1$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.63 (ABX system, $J_{AX} = 5.3$ Hz, 1H, 1-$\mathrm{CH_2}$), 3.08–3.14 (m, 1H, 2-CH), 5.93 (s, 2H, $\mathrm{OCH_2O}$), 6.63 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 6.64 (d, $J = 1.5$ Hz, 1H, ArH), 6.74 (d, $J = 7.8$ Hz, 1H, ArH); $\mathrm{C_{10}H_{13}NO_2 \cdot HCl}$ (215.7): calcd C 55.69, H 6.54, N 6.49, Cl 16.44; found C 55.62, H 6.56, N 6.49, Cl 16.39.

7b: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 0.97$ (t, $J = 7.4$ Hz, 3H, $\mathrm{CH_2C}H_3$), 1.29–1.58 (m, 2H, $CH_2\mathrm{CH_3}$), 1.79 (brs, 2H, $\mathrm{NH_2}$), 2.39 (ABX system, $J_{AB} = 13.4$, $J_{AX} = 8.5$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.72 (ABX system, $J_{AX} = 4.7$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.81–2.91 (m, 1H, 2-CH), 5.92 (s, 2H, $\mathrm{OCH_2O}$), 6.64 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 6.69 (d, $J = 1.5$ Hz, 1H, ArH), 6.74 (d, $J = 7.8$ Hz, 1H, ArH); $\mathrm{C_{11}H_{15}NO_2 \cdot HCl}$ (229.7): calcd C 57.51, H 7.02, N 6.10, Cl 15.43; found C 57.35, H 7.04, N 5.83, Cl 15.27.

7c: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 1.10$ (d, $J = 9.4$ Hz, 3H, $\mathrm{CH_3}$), 1.66 (s, 6H, $\mathrm{C(CH_3)_2}$), 2.29 (ABX system, $J_{AB} = 13.3$, $J_{AX} = 8.2$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.72 (ABX system, $J_{AX} = 5.1$ Hz, 1H, 1-$\mathrm{CH_2}$), 3.03–3.16 (m, 1H, 2-CH), 6.50–6.71 (m, 3H, ArH); $\mathrm{C_{12}H_{17}NO_2 \cdot HCl}$ (243.7): calcd C 59.13, H 7.44, N 5.75, Cl 14.54; found C 59.19, H 7.40, N 5.63, Cl 14.43.

7d: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 1.26$ (d, $J = 6.5$ Hz, 3H, $\mathrm{CH_3}$), 2.74 (ABX system, $J_{AB} = 13.7$, $J_{AX} = 7.5$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.85 (ABX system, $J_{AX} = 6.5$ Hz, 1H, 1-$\mathrm{CH_2}$), 3.43–3.51 (m, 1H, 2-CH), 3.86 (s, 3H, $\mathrm{CH_3O}$), 6.67 (dd, $J = 1.8$, 8.0 Hz, 1H, ArH), 6.77 (d, $J = 8.0$ Hz, 1H, ArH), 6.82 (d, $J = 1.8$ Hz, 1H, ArH)..

7e: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 1.06$ (d, $J = 6.1$ Hz, 3H, $\mathrm{CH_3}$), 2.30 (brs, 1H, NH), 2.41 (s, 3H, $\mathrm{NHC}H_3$), 2.55 (ABX system, $J_{AB} = 13.2$, $J_{AX} = 6.4$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.65 (ABX system, $J_{AX} = 6.8$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.67–2.80 (m, 1H, 2-CH), 5.93 (s, 2H, $\mathrm{OCH_2O}$), 6.63 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 6.68 (d, $J = 1.5$ Hz, 1H, ArH), 6.74 (d, $J = 7.8$ Hz, 1H, ArH); $\mathrm{C_{11}H_{15}NO_2 \cdot HCl}$ (229.7): calcd C 57.51, H 7.02, N 6.10, Cl 15.43; found C 57.26, H 7.01, N 6.07, Cl 15.44.

7f: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 1.06$ (d, $J = 6.2$ Hz, 3H, $\mathrm{CH_3}$), 1.90 (t, $J = 7.1$ Hz, 3H, $\mathrm{CH_2C}H_3$), 2.17 (s, 1H, NH), 2.49–2.80 (m, 4H, $CH_2\mathrm{CH_3}$, 1-CH_2), 2.80–2.94 (m, 1H, 2-CH), 5.93 (s, 2H, $\mathrm{OCH_2O}$), 6.63 (dd, $J = 1.6$, 7.9 Hz, 1H, ArH), 6.68 (d, $J = 1.6$ Hz, 1H, ArH), 6.74 (d, $J = 7.9$ Hz, 1H, ArH); $\mathrm{C_{12}H_{17}NO_2 \cdot HCl}$ (243.7): calcd C 59.13, H 7.44, N 5.75, Cl 14.54; found C 59.33, H 7.50, N 5.70, Cl 14.47.

7g: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 0.25$–0.54 (m, 4H, $\mathrm{CH}(CH_2)_2$), 1.09 (d, $J = 6.3$ Hz, 3H, $\mathrm{CH_3}$), 1.62 (s, 1H, NH), 2.00–2.07 (mc, 1H, $CH\mathrm{(CH_2)_2}$), 2.51 (ABX system, $J_{AB} = 13.5$, $J_{AX} = 6.5$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.68 (ABX system, $J_{AX} = 7.1$ Hz, 1H, 1-$\mathrm{CH_2}$), 2.97 (sext, $J = 6.3$ Hz, 1H, 2-CH), 5.93 (s, 2H, $\mathrm{OCH_2O}$), 6.63 (dd, $J = 1.5$, 7.8 Hz, 1H, ArH), 6.69 (d, $J = 1.5$ Hz, 1H, ArH), 6.74 (d, $J = 7.8$ Hz, 1H, ArH); $\mathrm{C_{13}H_{17}NO_2 \cdot HCl}$ (255.7): calcd C 61.05, H 7.09, N 5.48, Cl 13.86; found C 61.12, H 7.05, N 5.60, Cl 13.65.

7h: ^{1}H NMR (250 MHz, $\mathrm{CDCl_3}$): $\delta = 0.93$ (t, $J = 7.4$ Hz, 3H, $\mathrm{CH_2C}H_3$), 1.32–1.57 (m, 2H, $CH_2\mathrm{CH_3}$), 1.99 (s, 1H, NH), 2.38 (s, 3H, $\mathrm{NHC}H_3$), 2.50–2.68 (m, 3H, 1-$\mathrm{CH_2}$, 2-CH), 5.93 (s, 2H, $\mathrm{OCH_2O}$), 6.63 (dd, $J = 1.6$, 7.9 Hz, 1H, ArH), 6.68 (d, $J = 1.6$ Hz, 1H, ArH), 6.74 (d, $J = 7.9$ Hz, 1H, ArH); $\mathrm{C_{12}H_{17}NO_2 \cdot HCl}$ (243.7): calcd C 59.13, H 7.44, N 5.75, Cl 14.54; found C 59.12, H 7.42, N 5.70, Cl 14.57.

Acknowledgement: This work was generously supported by the Bundesministerium für Bildung und Forschung (Zentrales Schwerpunktprogramm Bioverfahrenstechnik, Stuttgart) and the Fonds der Chemischen Industrie. We would like to thank Prof. K.-A. Kovar and his co-workers (Universität Tübingen) for the determination of *ee* values of the amphetamines and helpful discussions.

Received: January 31, 1997 [F 592]

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