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

Franz Effenberger* and Jürgen Jäger

Abstract: A stereoselective synthesis of (S)-3,4-methylenedioxyamphetamine (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 (1R,2S)-4 were obtained with high diastereoselectivity by addition of Grignard reagents to the O-protected cyanohydrins (R)-3, transamination of the addition products A with primary amines, and hydrogenation of the imino intermediates B with NaBH₄. For the hydrogenation of the benzylid hydroxyl group in the 1,2-amino alcohols (1R,2S)-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 (4S,5R)-6, which were readily available by phosgenation of the amino alcohols (1R,2S)-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-Methylenedioxyamphetamine (MDMA), for example, commonly known as “Ecstasy”, has been reported to produce both stimulant and hallucinogenic-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, +) enan-

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[5] 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 (1R,2S)-amino alcohols. We were especially interested in the preparation of the 3,4-methylenedioxy compounds for psychotherapeutical applications.

**Results and Discussion**

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

![Scheme 1. Enzyme-catalyzed addition of HCN to aldehydes 1 to give (R)-cyano-hydrazins 2 and subsequent preparation of (1R,2S)-2-amino-1-aryl alcohols 4a-d and (1R,2S)-2-alkylamino-1-aryl alcohols 4e-h.](image)

In an enzyme-catalyzed addition of HCN to the O-protected 3,4-dihydroxybenzaldehydes 1, the corresponding cyano-hydrazins (R)-2 were obtained with high optical purity.\[^{11a, 13c, 14}\] Addition of Grignard compounds to the nitrile group of the O-silylated cyano-hydrazins (R)-3 led to the imino intermediates A. Direct hydrogenation of A with NaBH₄ and acidic workup yielded the N-unsubstituted 2-amino alcohols (1R,2S)-4a-d.\[^{12}\] The 2-alkylamino-1-aryl alcohols (1R,2S)-4e-h were accessible by treatment of the imino intermediates A with methanol, transamination with a primary amine 5, and subsequent hydrogenation of the N-alkylamino compounds B with NaBH₄.\[^{11a, 11c}\]

For the synthesis of the pharmacologically interesting amphetamines methylenedioxyamphetamine (MDA, “Love Drug”), methylenedioxyamphetamine (MDMA, “Ecstasy”), and methylenedioxyamphetamines (MDME, “Eve”), we used the hydroxy-protected 3,4-dihydroxybenzaldehydes piperonal (1a), 2,2-dimethyl-5-formyl-1,3-benzodioxol (1b), and 3-methoxy-methylenoxy-4-methoxybenzaldehyde (1c)\[^{14}\] as substrates in the (R)-oxynitrilase-mediated cyanohydride formation (Scheme 1). As previously reported, the (R)-cyano-hydrazins (R)-2a-b are available with ee values of 93–99 % and good chemical yields.\[^{11a, 11c}\] However, (R)-2c can only be obtained with 81 % ee.\[^{14}\] According to the published procedure,\[^{12b}\] the tri-methylisilyl protecting group was introduced in cyano-hydrazins (R)-2a-c yielding the O-silylated cyano-hydrazins (R)-3a-c with 39–60 % yield based on the respective aldehydes 1a-c. The results of the preparation of the (1R,2S)-2-amino alcohols (1R,2S)-4 from (R)-3 (Scheme 1) are summarized in Table 1.

| Table 1. Synthesis of (1R,2S)-2-amino-1-aryl alcohols (1R,2S)-4 from O-silylated (R)-cyano-hydrazins (R)-3. |
|---|---|---|---|---|---|---|---|---|---|---|
| (R)-3 | R⁵MgX | 5 | (1R,2S)-4 | Yield [%] | ee [%] | [α] | (c in MeOH) | M.p. °C |
| a | CH₃Mgl | -a | 51 | 95 | -12.5 (1.40) | 212 |
| b | C₆H₅MglBr | b | 45 | 90 | -29.0 (1.00) | 201 |
| c | CH₃Mgl | c | 38 | >95 | -15.2 (1.10) | 192 [d] |
| d | CH₃Mgl | d | 13 [c] | 90 | -10.0 (0.70) | 204 [d] |
| e | CH₃Mgl | a | 47 | 77 | -41.6 (0.80) | 223 [d] |
| f | CH₃Mgl | b | 47 | >95 | -28.0 (1.00) | 222 |
| g | CH₃Mgl | c | 57 | >95 | -26.6 (0.80) | 194 |
| h | C₆H₅MglBr | a | 44 | 92 | -31.6 (1.20) | 194 |

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

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

**Transformation of (1R,2S)-4 into (S)-amphetamines (S)-7 by catalytic hydrogenation of oxazolidiones (4S,5R)-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 (1R,2S)-ephedrine to (S)-ephedrine in acidic acetone/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-diacytylenephradine in ethanol.
with addition of triethylamine at room temperature. Hydrogen uptake was complete after only 3 hours, and we were able to isolate the corresponding N-acetylaminophenethyl 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 phosphines or other carboxylic acid derivatives, can be viewed as cyclic urethanes. The NH group incorporated in the oxazolidinone ring should be sufficiently activated for hydrogenation, and the carboxylic acid formed by hydrogenation should decarboxylate readily.

Based on the procedure described by M. M. Fodor et al.,[18a] the 1,3-oxazolidin-2-ones (4S,5R)-6 were prepared by reaction of 1,2-amino alcohols (1R,2S)-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 (4S,5R)-6 were isolated with excellent yields. The oxazolidinones (4S,5R)-6a, b, e-g were purified by recrystallization from dichloromethane/ petroleum ether, while compounds (4S,5R)-6c,d,h, which were obtained as oils, were purified by chromatography on silica gel. In the case of (1R,2S)-4d, the reaction proceeded slowly and was accompanied by formation of by-products. Moreover, the product (4S,5R)-6d partly decomposed during chromatography. The low specific rotation (Table 2) indicated partial racemization.

A method for determination of diastereomeric excess could not be developed so far. In all cases, however, 'H NMR spectra show only one diastereomer. The specific rotation of (4R,5S)-4-methyl-5-phenyl-1,3-oxazolidin-2-one, prepared analogously from (1S,2R)-(+)-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 (4S,5R)-6 to the (S)-amphetamines (S)-7 under the reaction conditions described above for the hydrogenation of diacetylmorphine (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 (4S,5R)-oxazolidinones 6 by catalytic hydrogenation.

<table>
<thead>
<tr>
<th>(4S,5R)-6</th>
<th>t/h</th>
<th>(S)-7-HCl</th>
<th>Yield/%</th>
<th>ee/%</th>
<th>a [α]D (c in H2O)</th>
<th>M.p./°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>3</td>
<td>a</td>
<td>89</td>
<td>&gt;95</td>
<td>+26.6 (1.40)</td>
<td>198</td>
</tr>
<tr>
<td>6b</td>
<td>3</td>
<td>b</td>
<td>92</td>
<td>98</td>
<td>+35.6 (1.10)</td>
<td>165(f)</td>
</tr>
<tr>
<td>6c</td>
<td>6</td>
<td>c</td>
<td>98</td>
<td>n.d.</td>
<td>+17.0 (0.80)</td>
<td>165(f)</td>
</tr>
<tr>
<td>6d</td>
<td>5</td>
<td>d [d]</td>
<td>90</td>
<td>30</td>
<td>-9.3 (1.00)</td>
<td>150(f)</td>
</tr>
<tr>
<td>6e</td>
<td>2</td>
<td>e</td>
<td>96</td>
<td>&gt;99</td>
<td>+17.9 (1.00)</td>
<td>187</td>
</tr>
<tr>
<td>6f</td>
<td>5</td>
<td>f</td>
<td>93</td>
<td>&gt;98</td>
<td>+14.3 (2.00)</td>
<td>204</td>
</tr>
<tr>
<td>6g</td>
<td>4</td>
<td>g</td>
<td>47</td>
<td>n.d.</td>
<td>+17.6 (1.00)</td>
<td>166</td>
</tr>
<tr>
<td>6h</td>
<td>5</td>
<td>h</td>
<td>89</td>
<td>&gt;95</td>
<td>+26.1 (1.00)</td>
<td>181</td>
</tr>
</tbody>
</table>

[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 (4S,5R)-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. 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. 1H NMR spectra were recorded on a Bruker AC 250 F (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 570A with FID, nitrogen 30 mL min⁻¹, glass column (2.3 m x 2 mm), phases OV-17, 17, 101, 225 (3–5 %) on chromorb W. Avicel cellulose and (+)-norpseudoephedrine 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 dry glassware. The following aldehydes were prepared according to known procedures: 2,2-dimethyl-3-formyl-1,3-benzodioxole (1b) from 3-bromo-2,2-dimethyl-1,3-benzodioxole [209,211] 3-methoxymethylencyclo-4-methoxbenzaldehyde (1e) [14].

**Silylation of (R)-cyanohydrins (R)-2 to (R)-7 [212] at 0 °C pyridine (1 equiv) was added to a solution of cyanohydrin (R)-2 [211,213,214] in dry diethyl ether followed by the dropwise addition of trimethylchlorosilane (1 equiv) 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.

**General procedure for the synthesis of (4S,5R)-1,3-oxazolidin-2-ones (4S,5R):** To an ice-cold solution of (1R,2S)-4 in dichloromethane (ca. 50 mm) and triethylamine (3–7 fold excess of 4) a 2 N 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 (MgSO₄), and the solvent removed. The residue was crystallized from dichloromethane/petroleum ether or chromatographed on silica gel with ethyl acetate/petroleum ether (7:3).

**General procedure for the synthesis of (1R,2S)-2-alkylaminol-1-aryloxy alcohols (1R,2S)-4-b:** 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 allyl halide in diethyl ether [213,214] 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 (20–30 mL) was added dropwise. The reaction mixture was stirred for 1.5 h at room temperature and cooled to -60 °C, and NaBH₄ added in portions. The reaction mixture was allowed to warm up to room temperature within 1 h. The product was isolated by filtration through a small pad of Celite, washed with ethanol and ethyl acetate. The crude extracts were washed (MgSO₄), concentrated, and the residue chromatographed on silica gel with THF/CH₂Cl₂ sat. ethanol (1:1) or ethyl acetate/CH₂Cl₂ sat. methanol (30:1). For purification the product ether was crystallized from diethyl ether/petroleum ether or precipitated as hydrochloride with ethereal HCI solution and recrystallized from ethanol/diethyl ether.

**4b:** 1H NMR (250 MHz, CDC₁₃): δ = 0.90–1.00 (m, 3H, CH₃CH₂H), 1.00–1.20 (m, 1H, CH₂CH₂), 1.30–1.60 (m, 1H, CH₂CH₂), 1.80 (bs, 3H, NH₂, OH), 2.85 (me, 1H, 1, 2-CH), 4.47 (d, 2J = 5.1 Hz, 1H, 1-CH), 5.95 (s, 2H, OCH₂O), 6.77 (d, 2J = 0.8 Hz, 2H, ArH), 6.82 (s, 1H, ArH), C₆H₅NO₂HCl (245.7): calcd C 53.77, H 6.56, N 5.70, Cl 14.43; found C 53.72, H 6.64, N 5.72, Cl 14.51.

**4d:** 1H NMR (250 MHz, CDC₁₃): δ = 1.00 (d, 2J = 6.5 Hz, 3H, CH₃), 3.16 (dq, 2J = 6.5, 1H, 1, 2-CH), 3.52 (s, 3H, CH₃), 4.44 (d, 2J = 5.0 Hz, 1H, 1-CH), 5.22 (s, 2H, OCH₂O), 6.68 (d, 2J = 1.7 Hz, 8.2 Hz, 1H, ArH), 6.90 (d, 2J = 1.7 Hz, 1H, ArH), 7.10 (d, 2J = 8.2 Hz, 1H, ArH).

**4e:** HCl: 1H NMR (250 MHz, D₂O): δ = 0.94 (d, 2J = 6.7 Hz, 3H, CH₃), 2.59 (s, 3H, NCH₂), 3.28 (bs, 2H, 2-CH), 5.07–5.09 (m, 1H, 1-CH), 6.01 (s, 2H, OCH₂O), 6.12 (d, 2J = 4.4 Hz, 1H, OH), 6.85–6.95 (m, 5H, ArH), 8.98 (bd, 2J = 22.0 Hz, 2H, NH₂), C₆H₅NO₂HCl (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:** 1H NMR (250 MHz, CDC₁₃): δ = 0.85 (d, 2J = 6.5 Hz, 3H, CH₃), 1.14 (t, 2J = 7.1 Hz, 3H, CH₂CH₂), 2.60–2.85 (m, 4H, NHCH₂CH₂), 2.90 (dq, 2J = 4.0, 6.5 Hz, 1H, 2-CH), 4.70 (d, 2J = 4.0 Hz, 1H, 1-CH), 5.94 (s, 2H, OCH₂O), 6.77 (d, 2J = 1.0 Hz, 2H, ArH), 6.85 (d, 2J = 0.5 Hz, 1H, ArH), C₆H₅NO₂HCl (259.7): calcd C 55.49, H 6.99, N 5.39, Cl 13.65; found C 55.30, H 7.06, N 5.38, Cl 13.48.

**4g:** 1H NMR (250 MHz, CDC₁₃): δ = 0.33–0.43 (m, 2H, CH₂), 0.44–0.54 (m, 2H, CH₂), 0.86 (d, 2J = 6.5 Hz, 3H, CH₃), 2.16 (m, 1H, NHCH₂), 3.00 (dq, 2J = 4.0, 6.5 Hz, 1H, 2-CH), 4.72 (d, 2J = 4.0 Hz, 1H, 1-CH), 5.94 (s, 2H, OCH₂O), 6.76 (d, 2J = 0.7 Hz, 2H, ArH), 6.84 (s, 1H, ArH), C₆H₅NO₂HCl (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: 1H NMR (250 MHz, D₂O): δ = 0.84 (d, 2J = 7.4 Hz, 3H, CH₂CH₂), 1.11–1.38 (m, 2H, CH₂CH₂), 2.40–2.51 (m, 1H, 1-CH), 4.72 (d, 2J = 4.2 Hz, 1H, 1-CH), 5.94 (s, 2H, OCH₂O), 6.77 (d, 2J = 1.0 Hz, 2H, ArH), 6.85 (s, 1H, ArH), C₆H₅NO₂HCl (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 catalytic hydrolysis of oxazolidinones (4S,5R)-6 to (S)-aminothiazolines (7): A vigorously stirred solution of (4S,5R)-6 (0.4–14 mmol) in ethanol containing 5% triethylamine was hydrolyzed 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 NEt3 in vacuo the residue was dissolved in diethyl ether, and amphetamine hydrochlorides precipitated by addition of ethereal HCl solution.

7a: H NMR (250 MHz, CDCl3): δ = 1.11 (d, J = 6.3 Hz, 3H, CH3), 1.65 (bs, 2H, NH), 2.24 (ABX system, JAB = 13.4, JAX = 8.1 Hz, 1H, 1-CH3), 2.63 (ABX system, JAX = 5.3 Hz, 1H, 1-CH3), 3.08–3.14 (m, 1H, 2-CH), 3.93 (s, 2H, OCH3), 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), C2H5NO2·HCl (229.7): cale 56.69, H 6.54, N 6.49, Cl 16.44; found C 56.52, H 6.56, N 6.49, Cl 16.39.

7b: H NMR (250 MHz, CDCl3): δ = 0.97 (t, J = 7.4 Hz, 3H, CH3(CH2)3), 1.29–1.58 (m, 2H, CH2CH2), 1.57 (bs, 2H, NH), 2.39 (ABX system, JAB = 13.4, JAX = 8.1 Hz, 1H, 1-CH3), 2.72 (ABX system, JAX = 5.1 Hz, 1H, 1-CH3), 3.03–3.16 (m, 1H, 2-CH), 5.60–6.71 (m, 3H, ArH), C2H5NO2·HCl (234.7): cale 59.13, H 7.44, N 5.75, Cl 14.54; found C 59.19, H 7.40, N 5.63, Cl 14.43.

7c: H NMR (250 MHz, CDCl3): δ = 1.26 (d, J = 6.5 Hz, 3H, CH3), 2.74 (ABX system, JAB = 13.7, JAX = 7.5 Hz, 1H, 1-CH3), 2.85 (ABX system, JAX = 6.5 Hz, 1H, 1-CH3), 3.43–3.51 (m, 1H, 2-CH), 3.86 (s, 3H, CH3O), 6.67 (dd, J = 1.8, 8.0 Hz, 1H, ArH), 6.77 (d, J = 8.0 Hz, 1H, 1-CH3), 6.82 (d, J = 1.8 Hz, 1H, ArH).

7d: H NMR (250 MHz, CDCl3): δ = 1.06 (d, J = 6.1 Hz, 3H, CH3), 2.30 (bs, 1H, NH), 2.41 (s, 3H, NHCH3), 2.55 (ABX system, JAB = 13.2), JAX = 6.4 Hz, 1H, 1-CH3), 2.65 (ABX system, JAX = 6.8 Hz, 1H, 1-CH3), 2.67–2.80 (m, 1H, 2-CH), 5.93 (s, 2H, OCH3), 6.63 (dd, J = 1.5, 7.8 Hz, 1H, ArH), 6.68 (d, J = 1.5 Hz, 1H, ArH), 6.74 (d, J = 7.9 Hz, 1H, ArH), C12H24NO4·HCl (279.7): cale 57.51, H 7.02, N 6.10, Cl 15.43; found C 57.26, H 7.01, N 6.07, Cl 15.44.

7e: H NMR (250 MHz, CDCl3): δ = 1.06 (d, J = 6.2 Hz, 3H, CH3), 1.90 (t, J = 7.1 Hz, 3H, CH3(CH2)3), 2.17 (s, 1H, NH), 2.49–2.80 (m, 4H, CH2CH1, 1-CH2), 2.80–2.94 (m, 1H, 2-CH), 5.93 (s, 2H, OCH3), 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), C12H24NO4·HCl (243.7): cale 59.13, H 7.44, N 5.75, Cl 14.54; found C 59.33, H 7.50, N 5.70, Cl 14.47.

7f: H NMR (250 MHz, CDCl3): δ = 0.25–0.54 (m, 4H, CH2CH3), 1.09 (d, J = 6.3 Hz, 3H, CH3), 1.62 (s, 1H, NH), 2.00–2.07 (m, 1H, CH2CH3), 2.51 (ABX system, JAX = 13.5, JAX = 6.5 Hz, 1H, 1-CH3), 2.68 (ABX system, JAX = 7.1 Hz, 1H, 1-CH3), 2.97 ( sext, J = 6.3 Hz, 1H, 1-CH3), 5.93 (s, 2H, OCH3), 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), C12H24NO4·HCl (255.7): cale 61.05, H 7.09, N 5.48, Cl 13.86; found C 61.12, H 7.05, N 5.60, Cl 13.65.

7g: H NMR (250 MHz, CDCl3): δ = 0.93 (t, J = 7.4 Hz, 3H, CH3(CH2)3), 1.32–1.57 (m, 2H, CH2CH1), 1.99 (s, 1H, NH), 2.38 (s, 3H, NHCH3), 2.50–2.68 (m, 3H, 1-CH2, 2-CH), 5.93 (s, 2H, OCH3), 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), C12H24NO4·HCl (243.7): cale 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 de novo of the amphetamine and helpful discussions.

Received: January 31, 1997 [F92]