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Forensic Science International 149 (2005) 181–192
Forensic Science International
www.elsevier.com/locate/forsciint

Determination of synthesis route of 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P) based on impurity profiles of MDMA

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Received 25 February 2004; received in revised form 10 June 2004; accepted 10 June 2004
Available online 27 August 2004

Abstract

In our study 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P or PMK) was prepared by two different routes, i.e. by oxidizing isosafrole in an acid medium and by 1-(3,4-methylenedioxyphenyl)-2-nitropropene reduction. The final product-MDP-2-P was subjected to GC/MS analysis. The intermediates and reaction by-products were identified and the 'route specific' impurities were established. The following impurities are the markers of the greatest importance: 1-(3,4-methylenedioxyphenyl)-1-propanone (compound 10, Table 2), 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone (compound 11, Table 2) and 2,2,4-trimethyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolane (compound 13, Table 2) (the 'oxidising isosafrole route') and *N*-cyclohexylacetamide (compound 3, Table 1), 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 15, Table 1) (the 'MDP-2-nitropropene reduction route'). Subsequently, MDMA was prepared by reductive amination of MDP-2-P using $NaBH_4$ as reducing agent (so-called 'cool method'). Impurities were extracted with *n*-heptane under alkaline conditions. The impurity profiles were obtained by means of GC/MS, some reaction by-products were identified by means of the EI mass spectra including low energy EI mass spectra and 'route specific' impurities were established. 4-Methyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolan-2-one (compound 22, Table 2), *N*-methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethaneamine (compound 18, Table 2), 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 15, Table 1) and *N*-cyclohexyloacetamide (compound 3, Table 1) were found to be the synthesis markers of greatest importance.

Keywords: MDMA; MDP-2-P; Reductive amination; Route specific impurities

1. Introduction

Impurity profiling of drugs can be used for two purposes-determination of synthesis route and comparative analysis of seizures of drugs. Impurities which are characteristic for particular synthetic route are called synthesis markers. A marker can be called 'ideal', if it emerges only in particular synthetic route, but this occurs very rarely. In most cases, the marker of one route emerges in other synthesis methods as well. For instance *N*-formylMDMA, which is known marker for Leuckart route, is also found in impurity profiles of MDMA prepared by reductive amination and bromination of safrole. Therefore, instead of individual compounds, the groups of markers should be considered for determination

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0379-0738/$ – see front matter
doi:10.1016/j.forsciint.2004.06.016

of synthetic route. By increasing number of informative synthesis markers for each synthesis method, possibility of a false identification of synthesis method is reduced.

Moreover, there is also an issue of 'availability of markers' in the impurity profiling process. The route specific markers could not appeared in the impurity profiles for several reasons, e.g. if drug is thoroughly purified after synthesis, the extraction of impurities is not efficient and/or if analytical technique, used to provide profiles, is not sensitive enough. In order to deal with the above problems successfully, identification of individual impurities is essential.

Out of synthetic drugs, amphetamine and methamphetamine have been thoroughly investigated in respect to the route specific impurities and comparative analysis. Numerous papers have been devoted to the route specific impurities in these drugs and the procedures of impurity profiling [1–6]. Other synthetic drugs, such as 3,4-methylenedioxyamphetamine (MDA) or 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) have not been sufficiently investigated so far [7–13].

In clandestine manufacture of MDMA the most popular synthesis route is reductive amination of 1-(3,4-methylenedioxyphenyl)-2-propanone (MDP-2-P or PMK) [5,7,14–17]. The present controlled status of MDP-2-P has resulted in increase in illegal production of this precursor. A variety of methods have been reported for the synthesis of MDP-2-P [14] and a few papers were devoted to the impurities in MDP-2-P [11,13]. Fig. 1 shows a summary of two most probable synthesis routes of MDP-2-P in clandestine production [13–15] which were also chosen by authors to synthesized MDP-2-P, i.e. synthesis of MDP-2-P from piperonal via 1-(3,4-methylenedioxyphenyl)-2-nitropropene (MDP-2-nitropropene) and oxidation of isosafrole in an acid medium. So far the first method was not yet investigated in respect to the route specific impurities, but some studies have been done concerning impurities produce in the second method [13].

Identification of individual impurities is particularly useful for both the determination of synthetic route of MDMA and comparative analysis of seized MDMA tablets. Knowledge about by-products and intermediates enables identification of all steps in a synthesis of MDMA as well as identification of precursors such as piperonal, isosafrole and MDP-2-P. These compounds are very often produced during the synthesis as by-products. Therefore their identification in impurity profiles of MDMA is not equivalent with their use as precursors. This fact was found during our research on route specific impurities of MDMA prepared by different synthesis methods, from which only some results are presented in this paper. For example MDP-2-P and isosafrole were undoubtedly identified in impurity profiles of MDMA synthesized by safrole bromination followed by methylamination of bromosafrole.

In this work impurities produced in synthesis of MDP-2-P by the methods mentioned above, and impurities in MDMA·HCl prepared by reductive amination (Fig. 1) were investigated and route specific markers were identified. By means of these markers, the synthetic route of MDP-2-P and MDMA could be determined.

2. Materials and methods

2.1. Chemicals and reagents

In synthesis the following reagents were used: formic acid (98%), hydrochloric acid (36–38%), methylene chloride, sodium hydroxide, acetic acid (99.5%), acetone, hydrogen peroxide (∼33%), sulfuric acid (95%), all POCh, Poland, analytical grade, piperonal (99%, Aldrich), isosafrole (97%, Aldrich), nitroehtane (96%, Aldrich), cyclohexylamine (99%, Aldrich), methylamine solution (40% aqueous, Aldrich), diethyl ether (anhydrous, >99%, A.C.S. Reagent), $NaBH_4$ (Aldrich, for synthesis).

In impurity profiling experiments the following reagents were used: carbonate buffer pH 10 (10.7 ml, 0.1 M NaOH, 50 ml 0.05 M $NaHCO_3$, 39.3 ml H_2O), *n*-heptane (Aldrich, HPLC grade), diphenylamine (Supelco, used as internal standard).

2.2. Synthesis

The following synthesis methods of MDP-2-P and MDMA have been chosen by the authors according to the preferences of the clandestine laboratories. The physical and spectral (IR, NMR) properties of all synthesized compounds were identical with the data reported formerly [18].

MDP-2-P was synthesized by two different routes, i.e. by oxidation of isosafrole in an acid medium and by reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene, which was previously prepared by condensation of piperonal and nitroethane. Those syntheses were performed according to the procedures described by Shulgin [15].

MDMA was prepared according to the following method.

2.2.1. Reductive amination with $NaBH_4$ (so-called 'cool method')

Aqueous solution (40%) of methylamine (2 ml) was added to a cold mixture of MDP-2-P (1.51 g) in MeOH (5 ml). The mixture was cooled to −20 °C and then $NaBH_4$ (30 mg) was slowly added. After dissolving of reductive agent, reaction mixture was left at −20 °C for 2 h. The addition of $NaBH_4$ was repeated three times, in portions of 30, 30 and 40 mg, and reaction mixture was left at −20 °C for 24 h. Methanol was evaporated, 10% HCl (10 ml) was added to a residue, and the solution was washed with CH_2Cl_2 (3 × 8 ml). The organic solution was extracted with 10% HCl, combined aqueous layers were alkalized with 25% NaOH (∼10 ml) and extracted with CH_2Cl_2 (3 ×10 ml). Combined extracts were dried over $MgSO_4$, evaporated, a residue was dissolved in Et_2O (18 ml) and dry HCl was

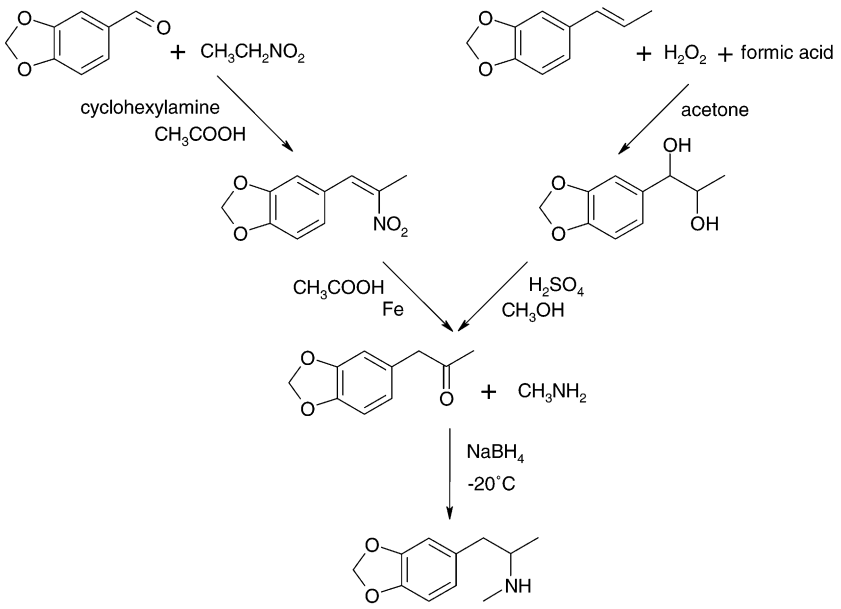


Fig. 1. Scheme of synthesis of MDP-2-P and MDMA.

passed through the solution. Precipitate of MDMA·HCl was filtered off and dried.

2.3. Extraction of impurities

Piperonal (0.015 g), isosafrole (0.015 g) and MDP-2-P (0.015 g) were dissolved in 200 μl of Et_2O and analyzed using GC/MS. Extraction of MDMA impurities was performed according to adopted method of amphetamine profiling used in Central Forensic Laboratory of the Police in Warsaw (Poland): a portion of 200 mg of MDMA·HCl was dissolved in 2 ml of carbonate buffer (pH 10), the solution was then vigorous shaken (25 min) following by addition of 200 μl of *n*-heptane containing diphenylamine as an internal standard, and then again shaken (25 min). The extracts were subjected to GC/MS analysis and impurity profiles were obtained. In the same way the extraction of impurities from MDP-2-nitropropene was performed.

2.4. Apparatus

GC/MS impurity profiles of MDMA were obtained according to adopted method of amphetamine profiling used in Central Forensic Laboratory of the Police in Warsaw (Poland). GC/MS analysis was carried out on Hewlett-Packard 6890 series gas chromatograph coupled to 5984B mass spectrometer. The deactivated, single taper splitless liner which had internal volume equal 900 μl and HP5-MS fused silica capillary column (30 m × 0.25 mm × 0.25 μm) were applied and helium 6.0 was used as a carrier gas (1.0 ml/min). The injection (2 μl) was made splitless by the autosampler. The following temperature program was applied: 50 °C maintained for 1 min, then ramped at 10 °C/min up to 150 °C, maintained 5.5 min, and again increased to 280 °C at 10 °C/min ramp, and maintained for the final 10 min. Mass spectrometer was operated in positive electron ionization mode (EI). The temperature of MS source was 230 °C, MS quadrupol −150 °C and transfer line −280 °C. A full-scan mass spectra 40–500 amu were obtained.

3. Results and discussion

In Tables 1 and 2 all compounds identified in the precursors, intermediates and final products were collected. The identification of all presented compounds was based on the EI mass spectra including low energy EI mass spectra.

3.1. Markers of MDP-2-P synthesis carried out by reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene

The compound 3 (Table 1), a product of the reaction of catalyst (cyclohexylamine) with acetic acid (Fig. 2), emerges in the first step of this synthesis and is present as

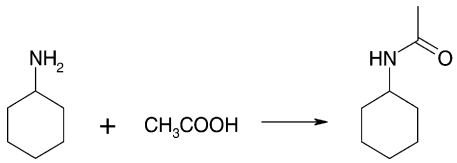
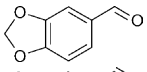
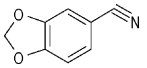
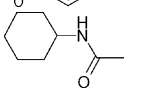
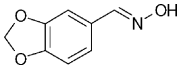
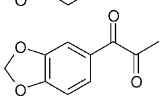
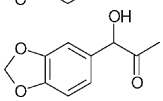
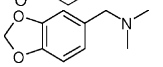
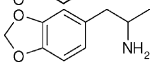
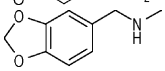
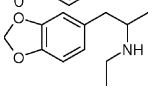
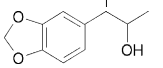
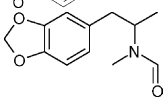
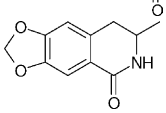
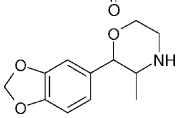
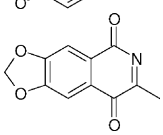


Fig. 2. One of the side-reactions occurring during the synthesis of MDP-2-nitropropene.

Table 1
Impurities identified in MDP-2-nitropropene, MDP-2-P, MDMA·HCl prepared from piperonal

	Structure of impurity	Synthesis of MDMA from piperonal			
		MW	Impurity name	Identified in	Eight-peak index of mass spectra
1		150	Piperonal	MDP-2-nitropropene, MDP-2-P, MDMA·HCl	149, 150, 32, 63, 44, 121, 43, 65
2		147	Piperonylonitrile	MDP-2-nitropropene	146, 147, 62,63, 89, 38, 88, 148
3		141	*N*-Cyclohexyl-acetamide	MDP-2-nitropropene, MDP-2-P, MDMA·HCl	60, 56, 43, 32,44, 141, 41, 98
4		165	Piperonal oxime	MDP-2-nitropropene	165, 122, 121, 146, 63,149, 148, 65
5		192	1-(3,4-Methylenedioxyphenyl)-1, 2-propanedione	MDP-2-P	149, 121, 65, 63, 150, 192, 91, 43
6		194	1-Hydroxy-1-(3,4-methylenedioxyphenyl)-2-propanone	MDP-2-P	151, 194, 121, 91, 43, 77, 152, 137
7		179	*N*,*N*-Dimethylpiperonylamine	MDMA·HCl	135, 179, 58, 136, 77, 178, 32, 51
8		179	3,4-Methylenedioxyamphetamine (MDA)	MDMA·HCl	44, 135, 136, 32, 77, 50, 43, 42
9		165	*N*-Methylpiperonylamine	MDMA·HCl	135, 164, 165, 136, 77, 42, 44, 51
10		207	*N*-Ethyl-MDA	MDMA·HCl	72, 77, 73, 42, 135, 51, 44, 70
11		180	1-(3,4-Methylenedioxyphenyl)-2-propanol	MDMA·HCl	135, 136, 180, 77, 32, 51, 45, 78
12		221	*N*-Formyl-MDMA	MDMA·HCl	86, 162, 58, 135, 77, 51, 30, 56
13		205	3-Methyl-6,7-methylenedioxy-3, 4-dihydroisoquinolin-1(2H)-one	MDMA·HCl	148, 190, 147, 205, 188, 204, 149, 89
14		221	2-Methyl-(6,7-methylenedioxyphenyl)-3-methylmorpholine	MDMA·HCl	71, 56, 149, 43, 70, 72, 149, 42
15		217	3-Methyl-6,7-methylenedioxyisoquinoline-1, 4-dione	MDP-2-P MDMA·HCl	217, 148, 147, 188, 89, 63, 218, 149, 91

an impurity in the precipitate of MDMA·HCl. The identification of this compound in impurity profiles of MDMA simultaneously with compounds 7, 8, 9, 14 and 15 (Table 1) indicates the synthesis of MDP-2-P by reduction of 1-(3,4-methylenedioxyphenyl)-2-nitropropene and MDMA by reductive amination.

In the above synthesis method cyclohexylamine could be replaced by some other amines as the catalysts, such as ethylamine, butylamine, pentylamine, etc. Hence, instead of compound 3, one could expect other *N*-alkylacetamide corresponding to amine used as catalyst. The compounds 7, 8, 9 and 14 were also found in impurity profiles of MDMA prepared by Leuckart method, but the compounds 3 and 15 (Table 1) were found in MDP-2-P and impurity profiles of MDMA only while MDP-2-P was prepared from piperonal, therefore their presence in seizures of MDMA tablets, simultaneously with these mentioned above, makes a strong proof of the use of this synthesis route under consideration.

Table 2
Impurities identyfied in isosafrole and subsequently in MDP-2-P and MDMA·HCl prepared from isosafrole

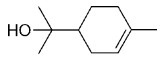
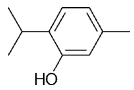
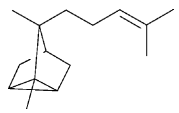
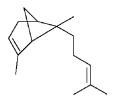
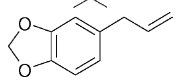
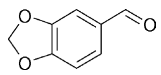
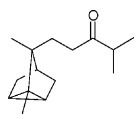
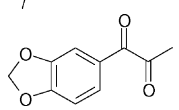
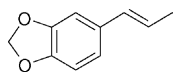
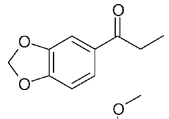
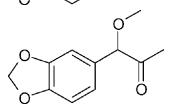
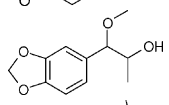
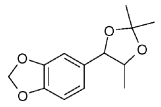
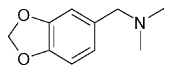
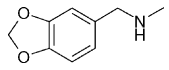
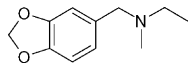
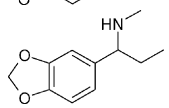
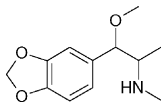
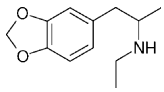
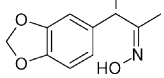
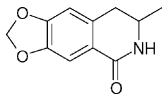
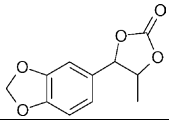
	Structure of impurity	Synthesis of MDMA from isosafrole			
		MW	Impurity name	Identyfied in	Eight-peak index of mass spectra
1		154	Terpineol (*p*-menth-1-en-8-ol)	Isosafrole	59, 93, 121, 136, 81, 43, 92, 67
2		150	2-Isopropyl-5-methylphenol (thymol)	Isosafrole	135, 150, 91, 136, 107, 77, 115, 105
3		204	1,7-Dimethyl-7-(4-methyl-3-pentenyl)-tricyclo[2.2.1.0^{2,6}]heptane	Isosafrole	94, 93, 95, 91, 107, 41, 121, 79
4		204	2,6-Dimethyl-6-(4-methyl-3-pentenyl)-bicyclo[3.1.1]hept-2-ene	Isosafrole	119, 93, 162, 91, 41, 107, 69, 77
5		162	Safrole	Isosafrole, MDP-2-P	162, 131, 104, 135, 103, 77, 78, 51
6		150	Piperonal	Isosafrole, MDP-2-P, MDMA·HCl,	149, 150, 121, 63, 65, 62, 91, 32
7		220	1-(2,3-Dimethyltricyclo[2.2.1.0^{2,6}]hept-3-yl)-4-methylpentan-3-one	MDP-2-P	149, 121, 65, 63, 192, 91, 43, 220
8		192	1-(3,4-Methylenedioxyphenyl)-1, 2-propanedione	MDP-2-P	149, 121, 65, 63, 150, 192, 91, 43
9		162	Isosafrole	MDP-2-P	162, 131, 104, 103, 161, 77, 78, 134
10		178	1-(3,4-Methylenedioxyphenyl)-1-propanone	MDP-2-P	149, 178, 121, 65, 150, 63, 91, 62
11		208	1-Methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone	MDP-2-P	165, 150, 149, 166, 119, 77, 63, 43
12		210	1-Methoxy-1-(3,4-methylenedioxyphenyl)-2-propanol	MDP-2-P	165, 150, 149, 135, 210, 77, 119, 107
13		223	2,2,4-Trimethyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolane	MDP-2-P	134, 192, 58, 179, 86, 178, 236, 163
14		179	*N,N*-Dimethylpiperonylamine	MDMA·HCl	135, 179, 58, 136, 77, 178, 32, 51
15		165	*N*-Methylpiperonylamine	MDMA·HCl	135, 164, 165, 136, 77, 42, 44, 51
16		193	*N*-Ethyl-*N*-methylpiperonylamine	MDMA·HCl	135, 193, 77, 136, 178, 72, 51, 42
17		193	*N*-Methyl-1-(3,4-methylenedioxyphenyl)-1-propaneamine	MDMA·HCl	164, 42, 165, 81, 77, 65, 63,135

Table 2 (*Continued*)

	Structure of impurity	Synthesis of MDMA from isosafrole			
		MW	Impurity name	Identyfied in	Eight-peak index of mass spectra
18		223	*N*-Methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)-ethaneamine	MDMA·HCl	58, 149, 165, 150, 59, 30, 77, 119
19		207	*N*-Ethyl-MDA	MDMA·HCl	72, 77, 73, 42, 135, 51, 44, 70
20		193	3,4-Methylenedioxybenzylmethylketoxime	MDMA·HCl	135, 193, 146, 77, 136, 51, 160, 105
21		205	3-Methyl-6,7-methylenedioxy-3,4-dihydroisoquinolin-1(2H)-one	MDMA·HCl	148, 190, 147, 205, 188, 204, 149, 89
22		222	4-Methyl-5-(3,4-methylenedioxyphenyl)-[1,3]dioxolan-2-one	MDMA·HCl	178, 134, 149, 163, 44, 43, 72, 222

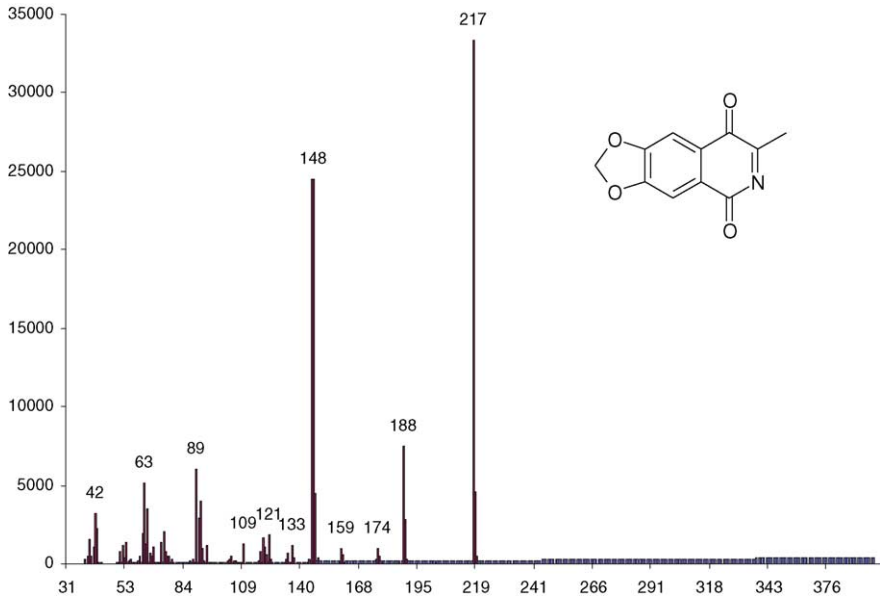


Fig. 3. Mass spectrum of 3-methyl-6,7-methylenedioxyisoquinoline-1,4-dione (compound 15 in Table 1).

The mass spectra of compounds 5, 6, 13, 14 and 15 are presented in Figs. 11, 12, 8, 9 and 3.

3.2. Synthesis markers of MDP-2-P synthesized by oxidizing isosafrole

The compound 13 and 22 (Table 2) are produce in reaction of oxidation of isosafrole by using acetone as a solvent [13]. Actually, the compound 13 have not been identified in impurity profiles of MDMA·HCl, because it was completely converted to MDP-2-P. However the compound 22 was only present in impurity profiles of MDMA·HCl.

The compound 18 is a product of the reaction of methylamine with compound 11 (Fig. 4). The compound 11 is produced as a by-product during the synthesis of MDP-2-P. The compound 3 (Table 2) which was identified in the

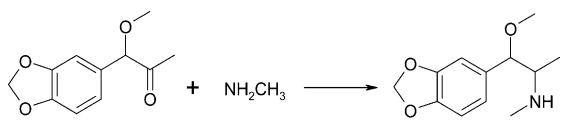


Fig. 4. One of the side-reactions occurring during the reductive amination of MDP-2-P prepared from isosafrole.

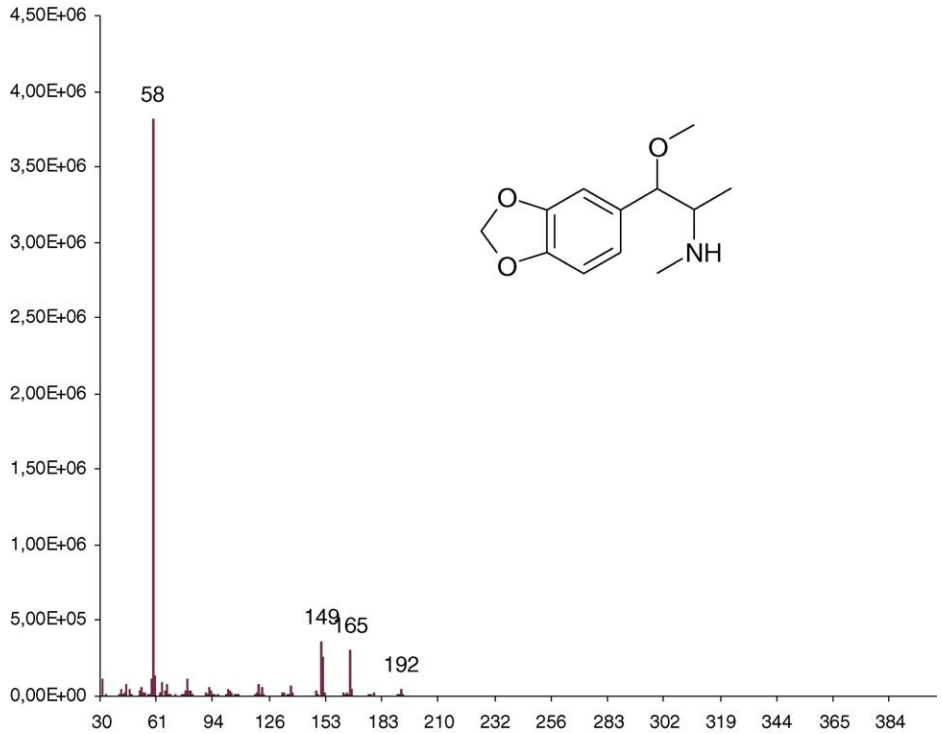


Fig. 5. Mass specrum of *N*-methyl-2-methoxy-1-methyl-2-(3,4-methylenedioxyphenyl)ethaneamine (compound 18 in Table 2).

commercially available isosafrole after oxidation gives compound 7 which is a marker of MDP-2-P synthesized from isosafrole. Compound 10 which is a by-product produced during the synthesis of MDP-2-P (Table 2) in the reaction with methylamine gives a corresponding amine, the compound 17 (Table 2). The compounds 14, 15 and 16 are the products of piperonal reaction with methylamine and its impurities (dimethylamine and methylethylamine). Their

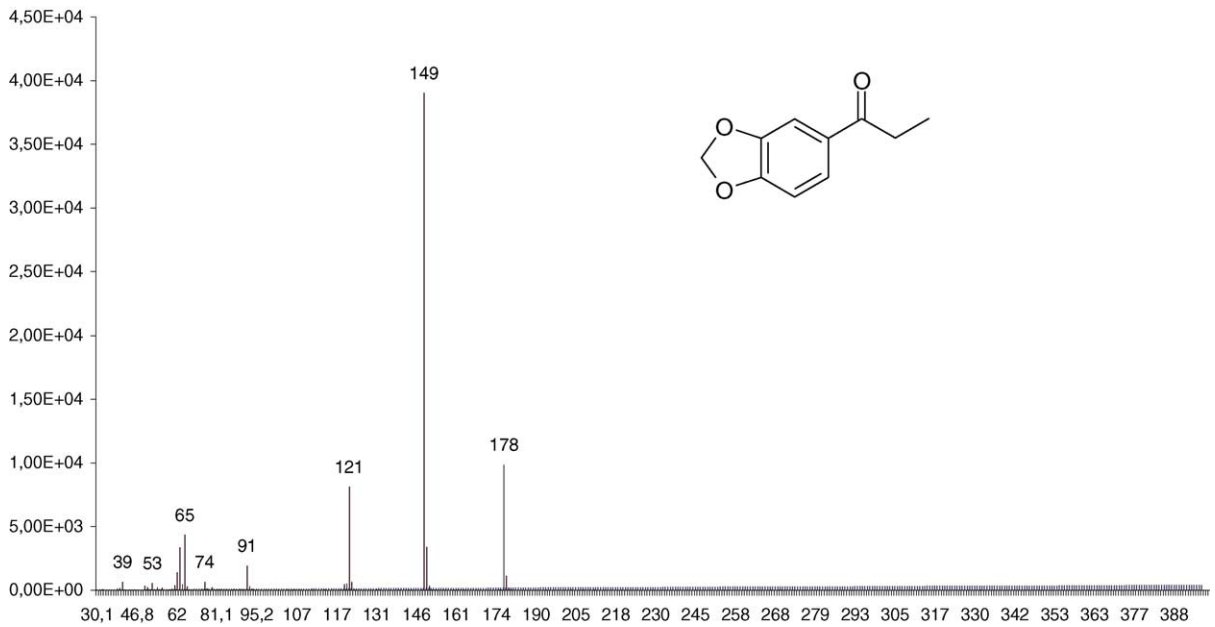


Fig. 6. Mass spectrum of 1-(3,4-methylenedioxyphenyl)-1-propanone (compound 10 in Table 2).

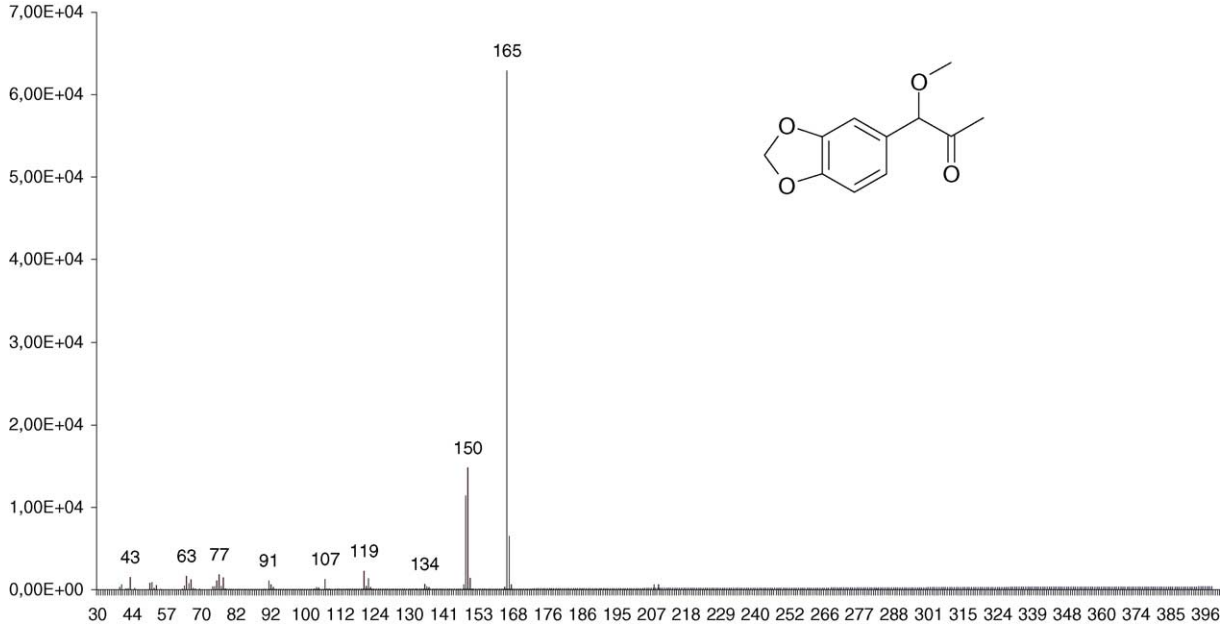


Fig. 7. Mass spectrum of 1-methoxy-1-(3,4-methylenedioxyphenyl)-2-propanone (compound 11 in Table 2).

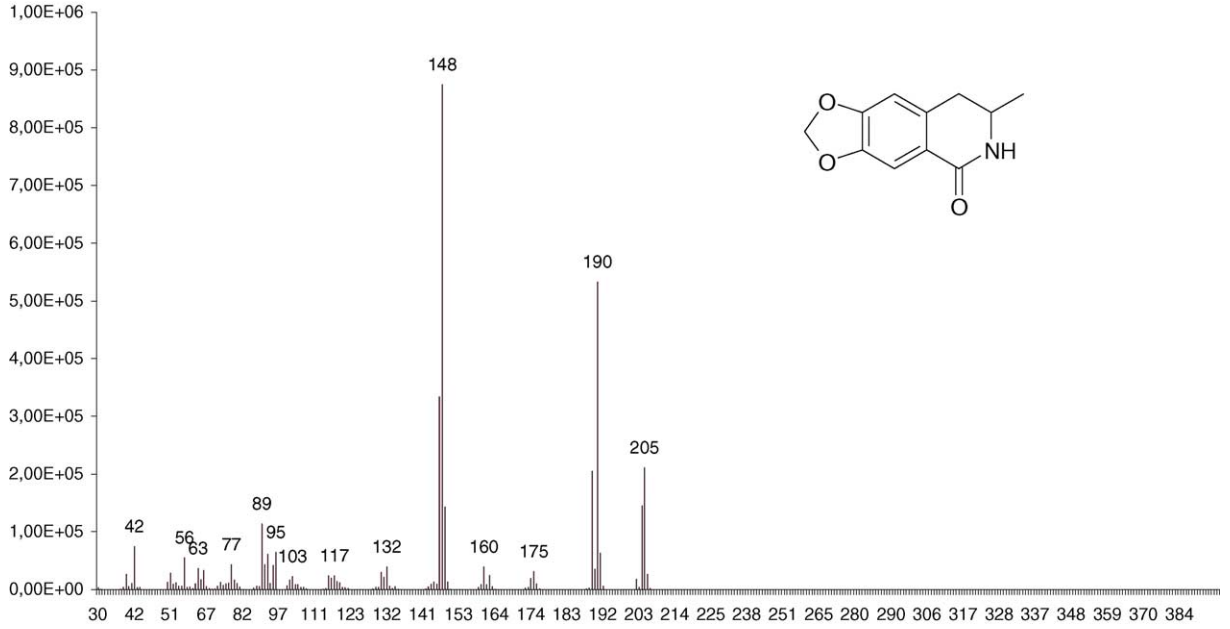


Fig. 8. Mass spectrum of 3-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolin-1(2H)-one (compound 13 in Table 1).

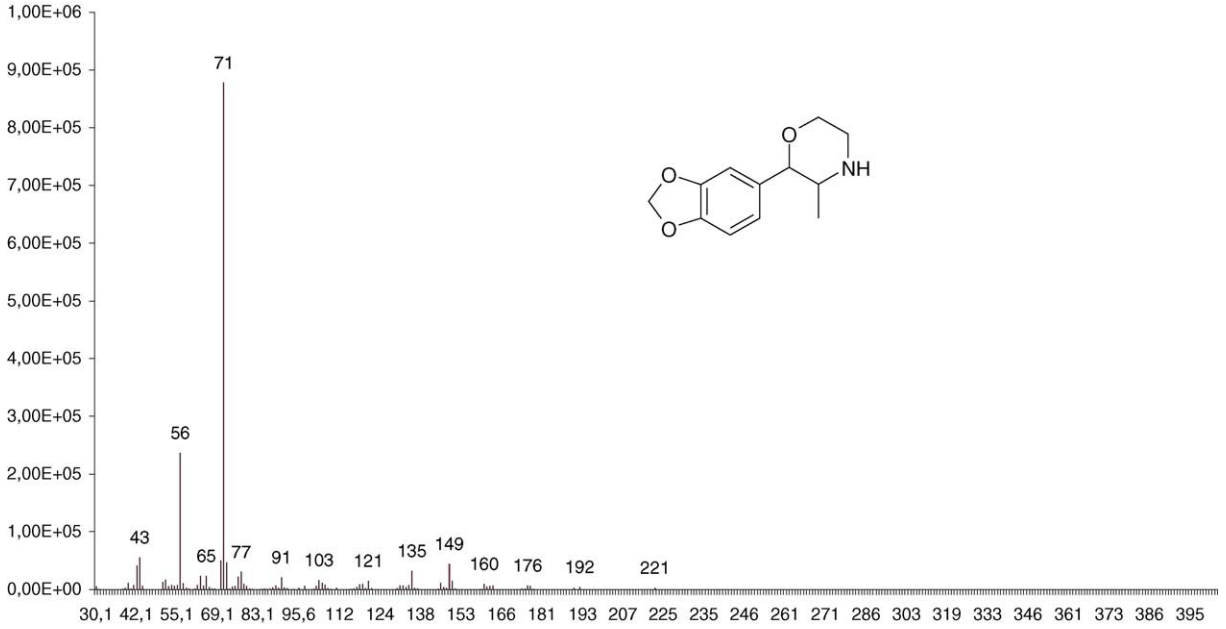


Fig. 9. Mass spectrum of 2-Methyl-(6,7-methylenedioxyphenyl)-3-methylmorpholine (compound 14 in Table 1).

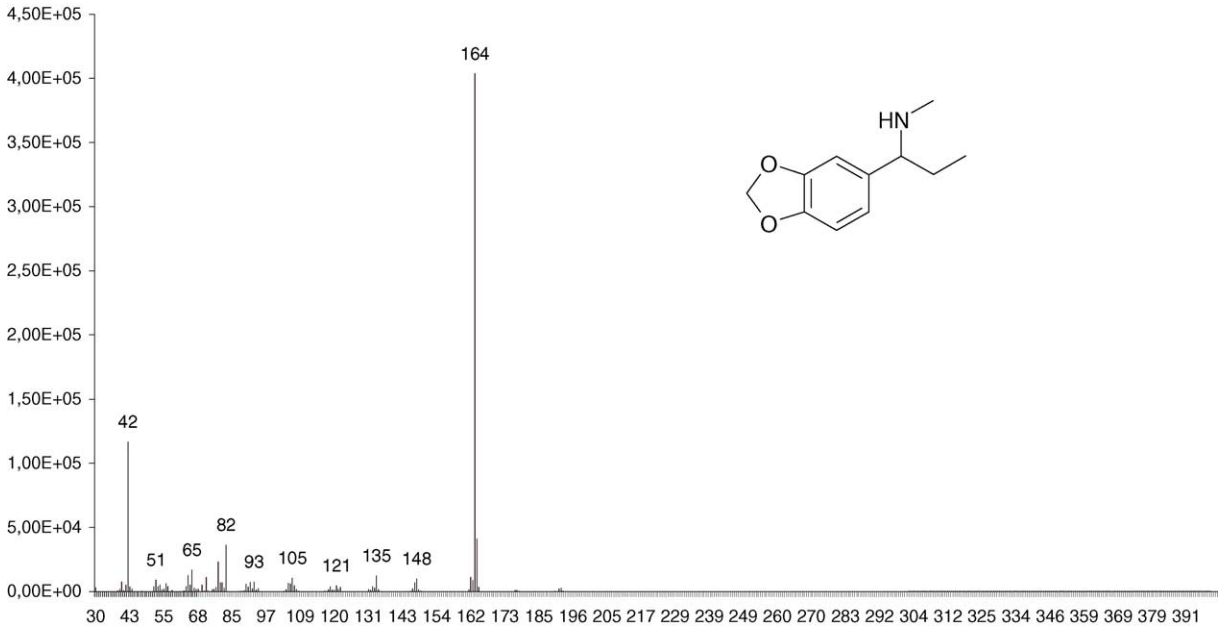


Fig. 10. Mass spectrum of *N*-methyl-1-(3,4-methylenedioxyphenyl)-1-propaneamine (compound 17 in Table 2).

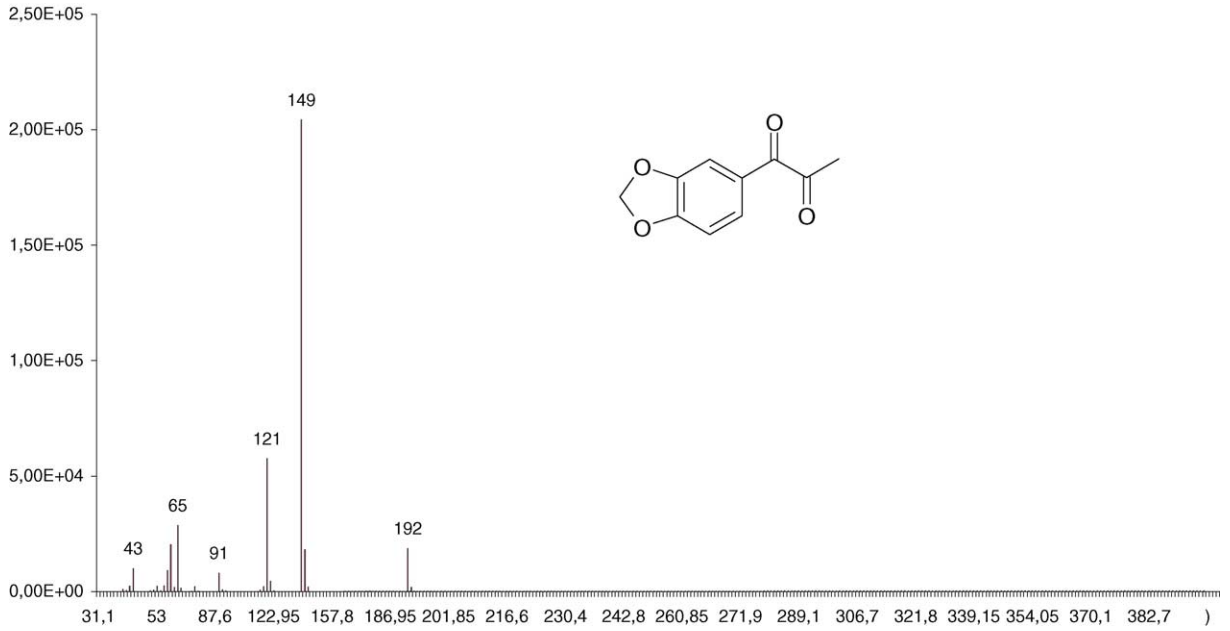


Fig. 11. Mass spectrum of 1-(3,4-methylenedioxyphenyl)-1,2-propanedione (compound 5 in Table 1).

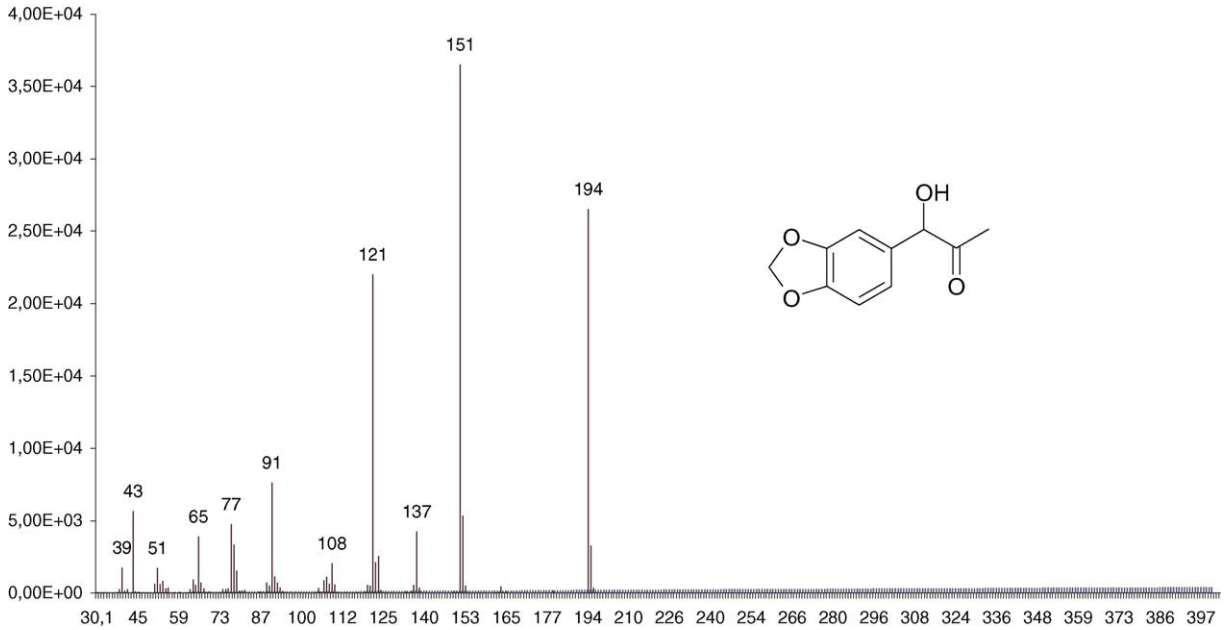


Fig. 12. Mass spectrum of 1-hydroxy-1-(3,4-methylenedioxyphenyl)-2-propanone (compound 6 in Table 1).

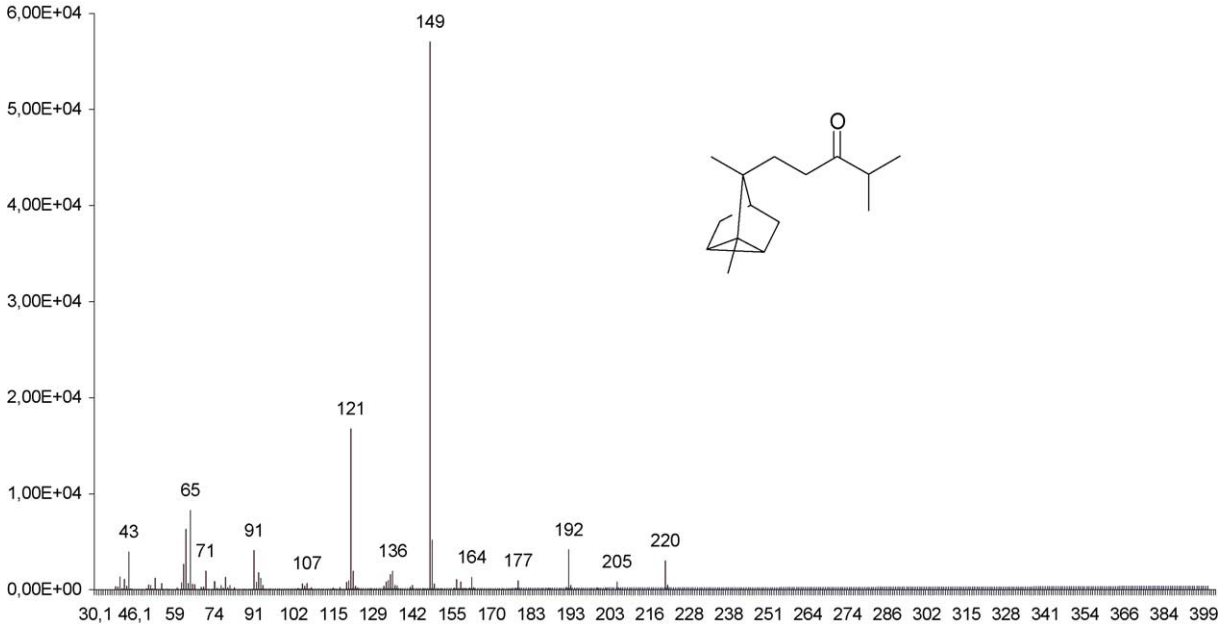


Fig. 13. Mass spectrum of 1-(2,3-dimethyltricyclo[2.2.1.$0^{2,6}$]hept-3-yl)-4-methylpentan-3-one (compound 7 in Table 2).

appearance in the impurity profile, together with compound 18 confirms the above synthesis route. The mass spectra of compounds 7, 10, 11, 17 and 18 are presented in Figs. 13, 6, 7, 10 and 5.

4. Conclusion

In summary, the synthesis markers of MDP-2-P prepared by two different synthesis routes were identified. These markers are present in impurity profiles of MDMA. On the basis of this fact, during the process of profiling of seized MDMA tablets, one can identify MDP-2-P as a precursor in the synthesis of MDMA. Moreover, the synthesis markers presented in this work enables determination of synthesis route of MDP-2-P.

Acknowledgments

This study was supported by a grant OT 00C 01024 from the Committee for Scientific Research, Poland.

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