Highly Enriched Mixtures of Methohexital Stereoisomers by Palladium-Catalyzed Allylation and Their Anaesthetic Activity[‡]

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The stereoselective Pd-catalyzed allylation of MBA [5-(2′-hex-3′-ynyl)-1-methylbarbituric acid] gives the commercial injection narcotic methohexital, which exists as four isomers: two diastereomeric pairs of enantiomers. The isomer composition produced depends on three stereochemical parameters: catalyst control, substrate control, and kinetic resolution. Judicious choice of these parameters allowed the synthesis of methohexital samples with greatly differing isomer compositions, and these samples were investigated with respect to their anaesthetic doses in rats. Some isomer compositions obtained were much more active than the commercially used drug and showed fewer side effects. As a consequence of the determination of the absolute configuration of the methohexital (S_bR_h) isomer, the unknown configuration of the trade product, the so-called α-racemate, can be established as (R_bS_h) and (S_bR_h).

Introduction

Methohexital [5-allyl-5-(2′-hex-3′-ynyl)-1-methylbarbituric acid, trade name Brevimytal®, Eli Lilly], is a short-time injection narcotic used as its Na salt in hospitals worldwide,[2−6] 1−2 mg/kg being necessary for a narcosis of about 10 min.[7,8] Methohexital has two configurationally stable asymmetric centers and so consists of four stereoisomers: two diastereomeric enantiomer pairs (Figure 1, right-hand side). Side effects of Brevimytal® are muscle twitches and muscle spasms observed during the narcosis and especially in the wake-up phase. It is known that these side effects result from certain diastereoisomers.[9,10] Furthermore, the individual methohexital isomers have shown differences in their anaesthetic activity.[9,10] As their classical resolution is preparatively lengthy and economically undesirable, we developed a strategy to produce highly enriched isomer mixtures of methohexital without classical resolutions.[11−13] In our approach, the stereoselectivity is introduced in the last synthetic step: the palladium-catalyzed allylation of the methohexital precursor 5-(2′-hex-3′-ynyl)-1-methylbarbituric acid, abbreviated MBA (Figure 1, left-hand side).

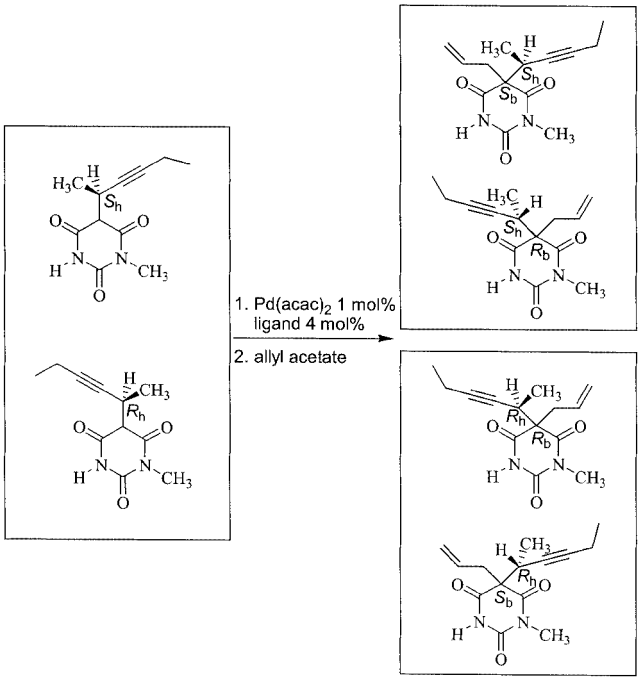

Figure 1. Pd-catalyzed allylation of MBA to give methohexital

[‡] Enantioselective Catalyses, 146. Part 145: Ref.[1]

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[‡‡] X-ray structure analysis.

MBA and Methohexital − Synthesis, Resolution, Specification of the Configuration, and GC Analysis

MBA is synthesized in five steps.[9,10,12−14] Similarly to methohexital, MBA also has two asymmetric centers. However, whereas the stereocenter in the side chain is configurationally stable, the stereocenter in the barbiturate ring is configurationally labile (keto-enol tautomerism).

MBA can be resolved with respect to its stable stereocenter in the side chain. While (−)-trimethyl[(*R*)-1-phenylethyl]ammonium hydroxide and *N*-methylquininium hydroxide as counterions did not give crystallizing salts with the MBA anions,[13] use of (−)-brucine as described in the literature[10] was successful, and (−)-MBA and (+)-MBA could be obtained in 97−100% purities.[13] If the asymmetric center in the 2′-hex-3′-yne side chain is denoted with the index h (= hexyne) and that in the barbiturate ring with index b (= barbiturate), and if the determination of the absolute configuration (see later) is included, the resolved MBA isomers must be designated (S_h)-(−)-MBA and (R_h)-(+)-MBA (Figure 1), each consisting of the two interconverting epimers (R_bS_h,S_bS_h) and (R_bR_h,S_bR_h).

The specification of the configuration in the hexyne side chain of methohexital according to the Cahn−Ingold−Prelog rules[15] is straightforward: C(CCC)−C(OON) > C(CCC)−C(CCC) > CH_3 > H. For the precursor MBA, however, it is a problem. If the tautomer with the acidic hydrogen atom at the tetrahedral carbon atom of the barbiturate ring is taken, the priority sequence is C(CCC) > C(CCH) > CH_3 > H. If, though, the tautomer with the acidic hydrogen atom at one of the oxygen atoms (as shown in Figure 1) is taken, the priority sequence changes to C(CCC)−C(OON) > C(CCC)−C(CCC) > CH_3 > H, due to the double bond formed in the barbiturate ring, resulting in an artificial reversal of the side chain configuration. The assignment of the configuration thus depends on which of the tautomers is assumed. An even worse situation arises if the configuration in the side chain is assigned for the MBA anion, formed when the acidic hydrogen atom is removed by a base. It is this anion that attacks the (η^3-allyl)Pd complex in the catalysis. Starting from the mesomeric formula of the MBA anion with the lone pair and the negative charge at the carbon atom of the barbiturate ring and starting from a mesomeric formula with the negative charge at one of the oxygen atoms give opposite configurations in the side chain, although the mesomeric formulas have no physical reality and contribute to the description of the same entity. This is a stereochemically interesting situation arising from a commercially important compound and not from an artificially constructed case. To enable us to use the same Cahn−Ingold−Prelog symbols for MBA and methohexital isomers with the same relative configuration in their side chains, we have chosen the enol form of MBA for the assignment of the side chain configuration.

GC analysis of MBA (CP-Chirasil-Dex-CB column) gives two well-separated peaks, each of which comprises two diastereomers with the same side chain configuration and differing ring configurations.[12,13] The assignment of the configuration to the stereocenter in the side chain can be made on the basis of the known absolute configuration of (S_bR_h)-methohexital (see below). In the catalytic allylation, (−)-MBA is converted into the (R_bS_h)- and (S_bS_h)-methohexital stereoisomers. Thus, (−)-MBA must have the (S_h) absolute configuration in the side chain. The other isomer is (R_h)-(+)-MBA. The first GC peak correlates to (S_h)-(−)-MBA and the second one to (R_h)-(+)-MBA.

The standard procedure for the palladium-catalyzed allylation of MBA (Figure 1) giving the results discussed below has been established previously.[12] In the Pd-catalyzed allylation, the labile stereocenter in the barbiturate ring of MBA is transformed into the stable quaternary stereocenter of methohexital.

The four stereoisomers of methohexital can be separated on a chiral GC column (Chiraldex B-PM, Figure 2). The peaks are assigned as follows. In the GC analysis of the crystals used for the determination of the absolute configuration [(S_bR_h) stereoisomer] only peak 4 (177 min) shows up. GC analysis of the products of the catalyses with enantiomerically pure (R_h)-(+)-MBA establishes that the isomers with (R_h) configuration in their side chains are peaks 1 (146 min) and 4 (177 min). Therefore, peak 1 corresponds to the (R_bR_h) isomer. The isomers with retention times 150 and 159 min (peaks 2 and 3) arise from (S_h)-(−)-MBA and have (S_h) configurations at the stereocenter in the side chain.

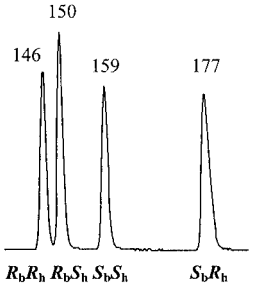

Figure 2. GC of the four isomers of methohexital

The methohexital isomer mixture shown in Figure 2 was obtained from the allylation of racemic MBA with a (triphenylphosphane)palladium catalyst. The diastereomer excess in this achiral catalysis is 10% (cat. 4, Table 1). The higher and identical intensities of peaks 2 and 4 show that they are enantiomers. Thus, peak 2 must correspond to the (R_bS_h) isomer. The lower intensity enantiomer pair consists of the (R_bR_h) (peak 1) and (S_bS_h) (peak 3) isomers. GC analysis of commercial Brevimytal® only shows peaks 2 and 4 (the enantiomers of the "α-racemate").

In the Pd-catalyzed allylation, racemic MBA, (−)-MBA, and (+)-MBA were all used as starting materials. Use of MBA resulted in the formation of all four methohexital isomers, whereas (S_h)-(−)-MBA and (R_h)-(+)-MBA only gave the (R_bS_h)/(S_bS_h) isomers (peaks 2/3) and the (R_bR_h)/(S_bR_h) isomers (peaks 1/4), respectively. The isomer distribution is influenced by three stereochemical parameters:

Table 1. Allylation of unresolved MBA: stereoisomeric excess, yields, and stereoselectivity factors for catalyses 1−4

Cat. no.	Ligand	A (R_bR_h)/(R_bS_h)/(S_bS_h)/(S_bR_h)	B *de* [%] (R_bS_h, S_bS_h)	C *de* [%] (S_bR_h, R_bR_h)	D *ee* [%] (R_bS_h, S_bR_h)	E *ee* [%] (S_bS_h, R_bR_h)	F "*ee*" [%][a][b] [b]	G Yield [%]	H *s*[c]
1a	**1**[d]	15:55:16:14	55 (R_bS_h)	3 (R_bR_h)	59 (R_bS_h)	3 (S_bS_h)	42 (S_h)	34	3.0
1b	**1**[d]	17:54:14:15	59 (R_bS_h)	6 (R_bR_h)	57 (R_bS_h)	10 (R_bR_h)	36 (S_h)	16	2.3
1c	**1**[e]	9:49:17:25	48 (R_bS_h)	39 (S_bR_h)	32 (R_bS_h)	30 (S_bS_h)	37 (S_h)	60	3.0
1d	**1**[e]	19:50:14:17	56 (R_bS_h)	5 (R_bR_h)	49 (R_bS_h)	15 (R_bR_h)	29 (S_h)	63	2.7
1e	**1**[e]	20:51:11:18	65 (R_bS_h)	5 (R_bR_h)	48 (R_bS_h)	29 (R_bR_h)	25 (S_h)	63	2.3
1f	**1**[e]	17:57:11:15	68 (R_bS_h)	6 (R_bR_h)	58 (R_bS_h)	21 (R_bR_h)	35 (S_h)	59	3.4
1g	**1**[e]	19:55:10:16	69 (R_bS_h)	9 (R_bR_h)	55 (R_bS_h)	31 (R_bR_h)	30 (S_h)	59	2.7
2a	**2**[d]	9:24:27:40	6 (S_bS_h)	63 (S_bR_h)	25 (S_bR_h)	50 (S_bS_h)	2 (S_h)	87	1.1
2b	**2**[d]	10:20:21:49	2 (S_bS_h)	66 (S_bR_h)	42 (S_bR_h)	35 (S_bS_h)	18 (R_h)	72	0.5
3	**4**[d]	8:22:27:43	10 (S_bS_h)	68 (S_bR_h)	32 (S_bR_h)	54 (S_bS_h)	2 (R_h)	94	−
4	PPh_3 [d]	27:33:27:33	10 (R_bS_h)	10 (S_bR_h)	−	−	−	52	−

[a] R_h = excess of R_h epimers, S_h = excess of S_h epimers. [b] "Combined enantiomeric excess" (see ref.[12]). [c] *s* = stereoselectivity factor. [d] Catalyses with $[Pd(acac)_2]$. [e] Catalyses with $[(\eta^3\text{-}C_3H_5)PdCl]_2$.

catalyst control (depending on the optically active ligand), substrate control (influence of the stereocenter in the side chain), and kinetic resolution (only for racemic MBA).

In the catalyses with (−)-MBA and (+)-MBA the products have the side chain configuration of the starting material. There is no kinetic resolution; stereoselectivity comes from catalyst control and side chain control. With racemic MBA there is catalyst control, but side chain control only in the *ee* values, and not in the *de* values. In addition, kinetic resolution comes into play and the isomer distribution becomes conversion-dependent. Thus, by use of suitable combinations of the three parameters, it is possible to synthesize methohexital mixtures of widely differing isomer composition without any prior classical resolution.

The allylation of MBA was scaled up by a factor of 10, with 5.0 g of MBA being used (catalysis 1 h) instead of 500 mg (standard procedure). The yield of 62% and the isomer distribution [(R_bR_h)/(R_bS_h)/(S_bS_h)/(S_bR_h) = 10.4:50.8:15.8:24.0] did not differ from the results obtained in smaller runs under standard conditions (catalyses 1a−1g, Table 1).

Allylation of Racemic MBA

Phosphaneimines derived from (2-formylphenyl)diphenylphosphane and optically active primary amines with a hydroxymethyl substituent and a large alkyl group at the asymmetric center had given the best stereoselectivities in the Pd-catalyzed allylation of barbiturates.[11,12] As large alkyl groups, isopropyl, *sec*-butyl and *tert*-butyl moieties had been used. The cyclohexyl derivatives **1** and **2** are new ligands of this type (Figure 3), prepared by Schiff base condensation of (2-formylphenyl)diphenylphosphane with the primary amines (*R*)-2-amino-2-cyclohexylethan-1-ol and (*S*)-2-amino-3-cyclohexylpropan-1-ol. The results of the catalyses with **1** and **2** as ligands are summarized in Table 1.

Because of the contribution of the kinetic resolution, the catalyses with unresolved MBA were conversion-dependent. Therefore, catalyses 1a and 1b (Table 1) were stopped at low conversion, whereas catalyses 1c−1g were carried through to about 60% conversion (column A). In all the catalyses 1 with ligand **1**, the (R_bS_h) isomer dominated the

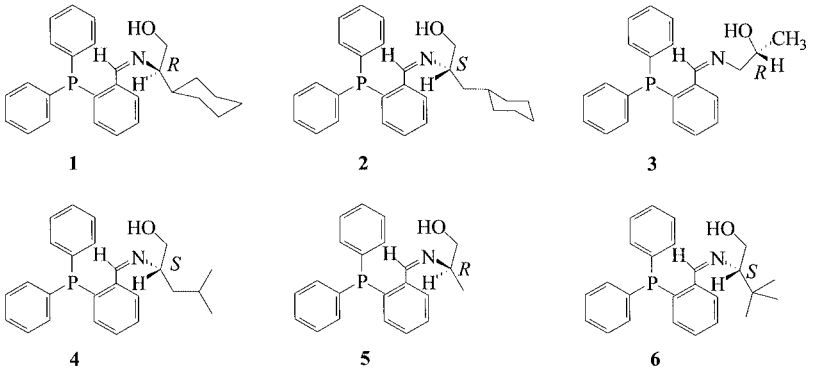

Figure 3. The phosphaneimine alcohols **1−6**

four-isomer mixture. In catalyses 2 with ligand **2**, however, the (S_bR_h) isomer took the lead.

In the Pd-catalyzed allylation of racemic MBA, the phosphaneimine ligand **1** gave a large diastereomeric excess with respect to the (S_h) epimers (column B). For the (R_h) epimers only a small diastereoselectivity was observed (column C). As was to be expected, the inversion of configuration at the chiral carbon atom in ligand **2** induced the preferential formation of the opposite enantiomers. Instead of (R_hS_h) (*de* = 59%) in catalysis 1, in catalyses 2a and 2b the (S_bR_h) isomer was formed with *de* = 63 and 66%. The *de* values, which are conversion-independent, reflect the catalyst and the side chain contributions.

As far as the enantioselectivities are concerned (columns D and E), ligand **1** produced the (R_bS_h) isomer in the enantiomer pair (R_bS_h,S_bR_h) with high selectivities, whereas the *ee* values obtained for the (S_bS_h,R_bR_h) pair were small at low levels of conversion, but increased during the reaction. In catalysis 2 the enantioselectivities of the two pairs of enantiomers were close together. The *ee* values reflect the catalyst control and the contribution of the kinetic resolution.

The influence of the kinetic resolution also shows up in the stereoselectivity factors *s*[16] (column H), which for ligand **1** were between 3.4 and 2.3. Calculation of the stereoselectivity factors requires the "combined enantioselectivities" (column F) and the conversion (column G). The "*ee*" value is the excess of the (R_h) epimers with respect to the (S_h) epimers (for definitions and formulas see ref.[12]).

In catalysis 1a, unchanged MBA was recovered in 55% yield and with 46% *ee* for (R_h)-(+)-MBA. From these data, a similar stereoselectivity factor $s = 3.7$ is calculated both for the remaining starting material MBA and for the product.[12,16]

It was investigated whether functionalization of the hydroxy group of the crucial hydroxymethyl substituent in ligand **4** (Figure 3) would improve the interaction with the incoming nucleophile and increase the enantioselectivity. The hydroxy group was converted into the methyl, 2-methoxyethyl, and 2,2-diethoxyethyl ethers, and also into the acetate ester. When these ligands were used in the Pd-catalyzed allylation of racemic MBA, enantioselectivities were negligible and diastereoselectivities were in the range of 5−10% only,[13] and so the stereoselectivities of the new ligands did not match those of ligand **4**, from which they were derived (cat. 3, Table 1). Poor results were also obtained with the ligands (2*R*)-(−)-1-({1-[2-(diphenylphosphanyl)phenyl]methylidene}amino)-2-propanol (**3**), (2*S*)-(−)-2-({1-[2-(diphenylphosphanyl)phenyl]methylidene}amino)-1-methoxy-4-methylpentane, and (2*R*)-(−)-1,1-diphenyl-2-({1-[2-(diphenylphosphanyl)phenyl]methylidene}amino)-2-pentanol.[12,13] Synthesis and characterization of the new ligands are described in refs.[12,13]

Samples of 200 mg of isomer mixtures obtained in catalyses 1c and 1f (Table 1) were recrystallized from hexane (12 mL), producing increases in the proportion of the dominating (R_bS_h) isomer and decreases in the share of the (S_bR_h) isomer, to which the pharmaceutical side-effects are attributed (see below). After two recrystallizations, the (R_bR_h)/(R_bS_h)/(S_bS_h)/(S_bR_h) isomer mixtures had changed from 9:49:17:25 (cat. 1c, Table 1) to 6:77:3:14 and from 17:57:11:15 (cat. 1f, Table 1) to 9:75:6:10 (yield about 50%).

The (R_bS_h,S_bR_h) pair of enantiomers was separated by achiral HPLC [HPLC Knauer, column Phenomex Luna

Table 2. Matched combinations of substrate (S_h)-(−)-MBA/(*R*)-configured ligand and (R_h)-(+)-MBA/(*S*)-configured ligand and mismatched combinations (S_h)-(−)-MBA/(*S*)-configured ligand

Cat. no.	Substrate	Ligand	(R_bS_h)/(S_bS_h)	(S_bR_h)/(R_bR_h)	*de* [%] (R_bS_h, S_bS_h)	*de* [%] (S_bR_h, R_bR_h)	Yield [%]
5a	(S_h)-(−)-MBA	PPh_3 [a]	59:41	–	18 (R_bS_h)	–	40
5b	(S_h)-(−)-MBA	PPh_3 [a]	60:40	–	20 (R_bS_h)	–	60
5c	(S_h)-(−)-MBA	PPh_3 [a]	60:40	–	20 (R_bS_h)	–	36
6a	(S_h)-(−)-MBA	(*R*)-**5**[a]	73:27	–	46 (R_bS_h)	–	–
6b	(S_h)-(−)-MBA	(*R*)-**5**[a]	73:27	–	46 (R_bS_h)	–	67
7a	(S_h)-(−)-MBA	(*R*)-**4**[a]	88:12	–	76 (R_bS_h)	–	64
7b	(S_h)-(−)-MBA	(*R*)-**4**[a]	87:13	–	74 (R_bS_h)	–	78
7c	(S_h)-(−)-MBA	(*R*)-**4**[b]	86:14	–	72 (R_bS_h)	–	67
7d	(S_h)-(−)-MBA	(*R*)-**4**[b]	86:14	–	72 (R_bS_h)	–	66
7e	(S_h)-(−)-MBA	(*R*)-**4**[b]	85:15	–	70 (R_bS_h)	–	68
8a	(R_h)-(+)-MBA	PPh_3 [a]	–	59:41	–	18 (S_bR_h)	43
8a	(R_h)-(+)-MBA	PPh_3 [a]	–	60:40	–	20 (S_bR_h)	40
9	(R_h)-(+)-MBA	(*S*)-**5**[a]	–	74:26	–	48 (S_bR_h)	65
10	(R_h)-(+)-MBA	(*S*)-**4**[a]	–	86:14	–	72 (S_bR_h)	70
11a	(R_h)-(+)-MBA	(*S*)-**6**[a]	–	87:13	–	74 (S_bR_h)	72
11b	(R_h)-(+)-MBA	(*S*)-**6**[a]	–	88:12	–	76 (S_bR_h)	88
11c	(R_h)-(+)-MBA	(*S*)-**6**[a]	–	88:12	–	76 (S_bR_h)	79
12a	(S_h)-(−)-MBA	(*S*)-**4**[a]	43:57	–	14 (S_bS_h)	–	50
12b	(S_h)-(−)-MBA	(*S*)-**4**[a]	52:48	–	4 (R_bS_h)	–	25
13a	(S_h)-(−)-MBA	(*S*)-**6**[a]	41:59	–	18 (S_bS_h)	–	20
13b	(S_h)-(−)-MBA	(*S*)-**6**[a]	40:60	–	20 (S_bS_h)	–	40
13c	(S_h)-(−)-MBA	(*S*)-**6**[a]	43:57	–	14 (S_bS_h)	–	46

[a] Catalyses with $Pd(acac)_2$. [b] Catalyses with $[(\eta^3\text{-}C_3H_5)PdCl]_2$.

10C18 (250 × 21.2 mm, 10 μm), acetonitrile/methanol/water (1:1:2), flow 8 mL/min, 25 °C] from 130 mg of the isomer mixture obtained in catalysis 1c, to afford 37 mg of the (R_bS_h,S_bR_h) enantiomers in a ratio of 73:27 (*ee* = 46%). Thus, in addition to Brevimytal® [(R_bS_h)/(S_bR_h) = 50:50] an (R_bS_h)/(S_bR_h) = 73:27 isomer mixture was available for tests.

Allylation of (S_h)-(−)-MBA and (R_h)-(+)-MBA

With (S_h)-(−)- and (R_h)-(+)-MBA as starting materials in the allylation reaction, the influence of side chain control and catalyst control could be studied without interference by the phenomenon of kinetic resolution. Catalyses 6 and 7 (Table 2) showed that the diastereomeric excess in the formation of the quaternary chiral center in the barbiturate ring increased from 46 to 70 and 76% on going from a small methyl group to a large *sec*-butyl group at the chiral center of the ligand. The same positive influence of large alkyl substituents was observed in catalyses 9 and 10 in Table 2. The *tert*-butyl-substituted ligand **6** afforded the highest diastereomeric excess of 74−76% (isomer ratio 88:12) in catalyses 11.

When the allylation started from (S_h)-(−)-MBA, side chain control with the achiral triphenylphosphane catalyst (cat. 5) gave a diastereomeric excess of 18−20% in the formation of the (R_b) ring configuration. In their chiral catalysts the (*R*)-configured ligands **5** and **4** increase the induction of the ring configuration (R_b) appreciably. The substrate (R_h)-(+)-MBA, together with the catalysts containing triphenylphosphane and the (*S*)-configured ligands, are exactly the mirror image situations favoring the (S_b) ring configuration (cat. 8−11, Table 2). Thus, catalyses 6 and 7 as well as catalyses 9−11 in Table 2 are matched combinations, in which side chain and catalyst control reinforce one another. Consequently, the (S_h)-(−)-MBA substrate/(*R*)-ligand catalyst and (R_h)-(+)-MBA substrate/(*S*)-ligand catalyst combinations give high diastereomeric excesses, numerically identical, but for opposite product enantiomers.

The mismatched combination is with the (*S*) configuration in the substrate and the (*S*) configuration in the ligand of the catalyst (and vice versa, Table 2, cat. 12 and 13). Catalyst control overcompensates the influence of the side chain and directs the catalyses to the (S_bS_h) stereoisomer. Because of the counteracting effects of substrate and catalyst control, though, only small isomer enrichments of ca. 10−20% are obtained.

The new phosphaneimine ligand **3** is an 1-amino-2-hydroxy derivative like the other ligands. However, it deviates from the successful lead structure in that, compared to **5**, the stereocenter is shifted from α to nitrogen atom to α to oxygen atom. With 14 and 13% *de* values the stereoselectivities of allylation with ligand **3** are only marginally higher than with triphenylphosphane. In combination with (S_h)-(−)- and (R_h)-(+)-MBA, **3** did not show double stereodifferentiation. Furthermore, conversion was slow.[13]

Starting from 100 mg of the isomer mixture obtained in catalyses 7c, the (R_bS_h) enantiomer was separated from its (S_bR_h) diastereomer by achiral HPLC [HPLC Knauer, column Phenomex Luna 10C18 (250 × 21.2 mm, 10 μm), acetonitrile/methanol/water (1:1:2), flow 8 mL/min, 25 °C] to afford 50 mg of the (R_bS_h) enantiomer (100% *ee*).

Absolute Configuration of Methohexital

The mixture of stereoisomers obtained from catalysis 11b (Table 2) was used for the determination of the absolute configuration of methohexital. Repeated precipitation and recrystallization from 2-propanol/water (2:1) resulted in the enrichment of the more soluble isomer in solution up to a diastereomeric purity of 98%. Colorless crystals suitable for X-ray analysis could be isolated from the solution in hexane after several weeks at 0 °C (Table 3).

Table 3. Crystal data, data collection, and structure refinement for (S_bR_h)-methohexital

Compound	(S_bR_h)-methohexital
Crystal data:	
Empirical formula	$C_{14}H_{18}N_2O_3$
Formula mass [g/mol]	262.30
Crystal size [mm]	0.88 × 0.64 × 0.36
Crystal system	triclinic
Space group	*P*1
a [Å]	8.0250(8)
b [Å]	8.3162(3)
c [Å]	13.1094(17)
α [°]	78.580(6)
β [°]	72.622(9)
γ [°]	63.302(6)
Volume [Å^3]	743.85(13)
Z, $D_{calcd.}$ [Mg m^{-3}]	2, 1.171
Absorption coefficient	0.68 mm^{-1}
Data collection:	
Measurement device type	Enraf−Nonius CAD-4 diffractometer
Measurement method	ω/2Θ
Temperature [K]	297(1)
Radiation (monochromated)	Cu-$K_α$ (graphite), 1.54180 Å
$Θ_{min.}$, $Θ_{max.}$ [°]	3.54, 70.76
Index ranges	$-9 \le h \ge 9$ $-9 \le h \ge 10$ $-16 \le h \ge 16$
Nos. refl. collected/unique	5618/5618
Reflections [$I > 2σ(I)$]	5569
Absorption correction	ψ-scan
Refinement:	
Refinement method	full-matrix least squares on F^2
Hydrogen treatment	mixed
Data, restraints, parameters	5618, 3, 352
Final *R*, *wR*2 [$I > 2σ(I)$]	*R*1 = 0.0431, *wR*2 = 0.1255
R, *wR*2 (all data)	*R*1 = 0.0432, *wR*2 = 0.1257
Absolute structure parameter	−0.18(17)
Min./max. resd. density [e/Å^{-3}]	−0.149, 0.299

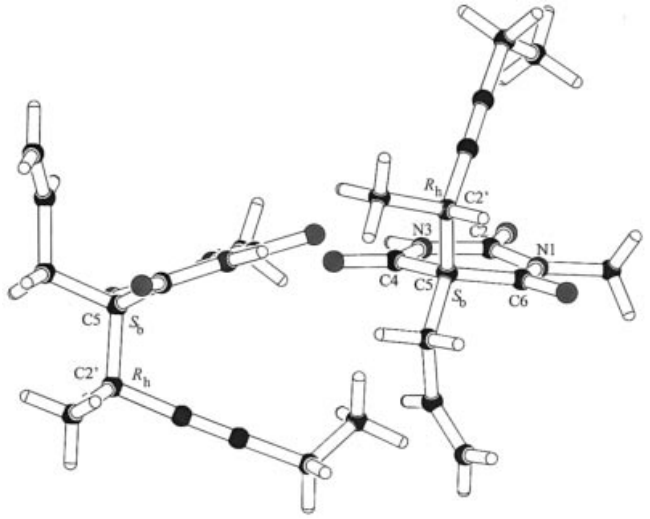

Figure 4. Structure of the methohexital (S_bR_h) isomer in the solid state

The unit cell consists of two independent molecules. The crystal system is triclinic (space group $P1$). Figure 4 shows that the barbiturate ring is almost planar. The maximum deviation from the plane is 0.06 Å at the tetrahedral ring carbon atom C5. The allyl group and the hexyne side chain are orientated below and above the barbiturate ring. The latter covers one side of the ring.

The use of monochromated Cu-K_α radiation gave an anomalous dispersion large enough for the determination of the absolute configuration. The Flack parameter (absolute structure parameter) is −0.18(17). The stereogenic center in the 2′-position of the hexyne side chain has the (R_h) absolute configuration and the chiral center in the barbiturate ring (S_b) in both independent molecules.

In combination with the GC base-line separation of the four methohexital isomers, it was now possible to establish the previously unknown absolute configuration of the commercially used anaesthetic Brevimytal®. It consists of a racemic mixture of the (S_bR_h) and (R_bS_h) stereoisomers.

Determination of the Anaesthetic Doses of Methohexital Stereoisomer Mixtures in Rats

The common anaesthetic Brevimytal® is applied intravenously as the sodium salt, and so the mixtures of the methohexital stereoisomers were also converted into their sodium salts. These were obtained by addition of an equimolar amount of 0.1 M NaOH and removal of the solvent.

During a 5−10 min Isofluran (Florane®) narcosis an intravenous entry was attached at the paw of a Sprague-Dawley rat. The animal was allowed to recover for at least 1 h before methohexital was applied, in order to avoid any influence of Isofluran. Then, intravenous injection of the aqueous methohexital salt solution (10 mg/ml) into the immobilized rat[12,17] was started, with a flow rate of 3.0 mg/min·kg.

The anaesthetic dose (AD) was determined by the corneal stimulus technique.[18] With the beginning of narcosis the eyelid stopped closing. For each experiment a new rat was used.

After a series of screening tests, the stereoisomer mixtures of catalysis 1c (two additional recrystallizations) in Table 1 [(R_bR_h)/(R_bS_h)/(S_bS_h)/(S_bR_h) = 6:77:14:3], catalysis 6b in Table 2 [(R_bS_h)/(S_bR_h) = 73:27], catalyses 7a and 7b in Table 2 [(R_bS_h)/(S_bS_h) = 88:12 and 87:13] and catalysis 11b in Table 2 [(S_bR_h)/(R_bR_h)= 88:12] were tested extensively. As a reference Brevimytal® [(S_bR_h)/(R_bS_h) = 50:50] was used (Table 4).

With the mixture of catalysis 7a (Table 2) narcosis was complete after an average time of 8.9 min. The calculated average AD was 26.6 mg/kg. For the mixture of 7b the average AD dose was 27.0 mg/kg. With the commercially used Brevimytal®, narcosis could only be achieved after 16.5 min and the AD was 50.0 mg/kg, almost twice as high as with samples of catalyses 7a and 7b (Table 2). The sample of catalysis 11b (Table 2) was similar to Brevimytal® (AD, 47.4 mg/kg, narcosis after 15.8 min). The average dose for the mixture of catalysis 1c (Table 2) was 30.3 mg/kg and for the mixture of catalysis 6b (Table 2) it was 37.3 mg/kg.

In addition to the anaesthetic doses, the side effects of methohexital were investigated. During recovery from the narcosis, muscle twitches and muscle spasms were observed for Brevimytal® [(S_bR_h)/(R_bS_h) = 50:50], and also for the sample of catalysis 11b (Table 2) [(S_bR_h)/(R_bR_h) = 88:12]. The sample of catalysis 6b (Table 2) [(R_bS_h)/(S_bR_h) = 73:27] showed fewer side-effects than Brevimytal®. However, the sample of catalysis 7a (Table 2) [(R_bS_h)/(S_bS_h) = 88:12] did not show any effects of this kind. By comparing the stereoisomeric compositions of the four samples, the side-effects of Brevimytal® could clearly be attributed to the (S_bR_h) stereoisomer.

Catalysis 1c in Table 1 shows that it is possible to start the allylation with the racemic substrate MBA and the ligand **1** and to produce a methohexital mixture that contains the stereoisomer (R_bS_h) enriched up to 55%, the other isomers being present only up to a maximum of 16%. Samples highly enriched in the (R_bS_h) isomer can thus be

Table 4. Methohexital stereoisomer mixtures and average anesthetic doses (AD)

Catalysis no.	**1c**	**6b**	**7a**	**7b**	**11b**	Brevimytal®
Stereoisomers	(R_bR_h)/(R_bS_h)/(S_bS_h)/(S_bR_h) 6:77:3:14[a]	(R_bS_h)/(S_bR_h) 73:27[b]	(R_bS_h)/(S_bS_h) 88:12	(R_bS_h)/(S_bS_h) 87:13	(S_bR_h)/(R_bR_h) 88:12[b]	(R_bS_h)/(S_bR_h) 50:50
Average AD [mg/kg]	30.3	37.3	26.6	27.0	47.4	50.0

[a] After two recrystallizations. [b] After chiral HPLC separation.

prepared without a tedious classical resolution. Previous investigations had shown that similar mixtures even with a smaller content of (S_bR_h) gave high anaesthetic activity.[12]

Experimental Section

General: The instruments used were the same as described in the preceding papers.[11,12] All the syntheses and catalytic reactions were carried out with dried solvents under nitrogen. Palladium(II) acetylacetonate and allyl acetate (Merck) were used without further purification. NEt_3 (Merck) was dried with CaH_2 and distilled. (2-Formylphenyl)diphenylphosphane was prepared according to the literature.[19−21] (*S*)-Phenylalanine was hydrogenated to (*S*)-(−)-2-amino-3-cyclohexylpropionic acid as described in the literature.[22] The same procedure was used to convert (*R*)-(−)-phenylglycine into (*R*)-(−)-2-amino-2-cyclohexylacetic acid. Reduction with BH_3·THF gave the amino alcohols (*S*)-(−)-2-amino-3-cyclohexylpropan-1-ol and (*R*)-(−)-2-amino-2-cyclohexylethan-1-ol.[23]

(*S*)-(−)-2-Amino-3-cyclohexylpropan-1-ol: Colorless liquid (70%). ^{1}H NMR: δ = 0.72−1.02 (m, 2 H, C_6H_{11}), 1.03−1.48 (m, 11 H, C_6H_{11}, $CH_2C_6H_{11}$), 1.89 (s, 3 H, OH, NH_2), 2.88−2.99 (m, 1 H, $CHNH_2$), 3.22 (dd, ^2J = 10.5, ^3J = 8.1 Hz, 1 H, CH_2OH), 3.56 (dd, ^2J = 10.5, ^3J = 3.8 Hz, 1 H, CH_2OH) ppm. IR (KBr): $\tilde{\nu}$ = 3310 (ν_{O-H}, ν_{N-H}), 1600, 1550 cm^{-1} (δ_{N-H}).

General Procedure for the Preparation of the Phosphaneimines: The optically active amino alcohol (2.54 mmol) was dissolved in the minimum possible amount of THF. At 0 °C, a solution of (2-formylphenyl)diphenylphosphane (2.12 mmol; 615 mg) in THF (20 mL) was added. The reaction mixture, while warming up to room temperature, was stirred for 12 h and dried with Na_2SO_4. Activated charcoal was added and filtered off after 10 min. The solvent was removed and the residue was dried and recrystallized as described for the individual phosphaneimines.

(2*R*)-(+)-2-Cyclohexyl-2-({1-[2-(diphenylphosphanyl)phenyl]methylidene}amino)ethanol (1): This compound was obtained from (*R*)-(−)-2-amino-2-cyclohexylethan-1-ol (365 mg, 2.54 mmol) and (2-formylphenyl)diphenylphosphane (615 mg, 2.12 mmol). Recrystallization was from petroleum ether (boiling range 40−60 °C). Colorless solid (446 mg, 35%), m.p. 86−88 °C. $[\alpha]_D^{r.t.}$ = +75, $[\alpha]_{578}^{r.t.}$ = +81, $[\alpha]_{546}^{r.t.}$ = +91, $[\alpha]_{436}^{r.t.}$ = +151 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR: δ = 0.53−0.63 (m, 1 H, C_6H_{11}), 0.76−0.89 (m, 1 H, C_6H_{11}), 0.89−1.06 (m, 2 H, C_6H_{11}), 1.09−1.18 (m, 2 H, C_6H_{11}), 1.30−1.39 (m, 1 H, C_6H_{11}), 1.48−1.70 (m, 4 H, C_6H_{11}), 1.96 (br. s, 1 H, OH), 2.89 (ddd, ^3J = 7.4, ^3J = 7.1, ^4J = 3.3 Hz, 1 H, CHN), 3.54 (dd, ^2J = 11.1, ^3J = 3.3 Hz, 1 H, CH_2OH), 3.67 (dd, ^2J = 11.1, ^3J = 7.1 Hz, 1 H, CH_2OH), 6.88 (ddd, ^3J = 7.7, $^3J_{HP}$ = 4.4, ^4J = 1.3 Hz, 1 H, Ar-H^6), 7.19−7.36 (m, 11 H, H_{ar}), 7.42 (ddd, ^3J = 7.6, ^3J = 7.4, ^4J = 1.3 Hz, 1 H, H_{ar}), 7.78 (ddd, ^3J = 7.6, $^3J_{HP}$ = 3.8, ^4J = 1.4 Hz, 1 H, Ar-H^3), 8.57 (d, $^4J_{HP}$ = 3.9 Hz, 1 H, HC=N) ppm. ^{31}P{^{1}H} NMR: δ = −9.19 ppm. IR (KBr): $\tilde{\nu}$ = 3400 (ν_{O-H}), 1640 cm^{-1} ($\nu_{C=N}$). MS (FD/CH_2Cl_2): *m*/*z* (%) = 415.5 (100) [M]. $C_{27}H_{30}$NOP (415.31): calcd. C 78.05, H 7.27, N 3.37; found C 77.58, H 7.27, N 3.35.

(2*S*)-(−)-2-Cyclohexyl-2-({1-[2-(diphenylphosphanyl)phenyl]methylidene}amino)ethanol (2): This compound was obtained from (*S*)-(−)-2-amino-3-cyclohexylpropan-1-ol (400 mg, 2.54 mmol) and (2-formylphenyl)diphenylphosphane (615 mg, 2.12 mmol). Recrystallization was from petroleum ether (boiling range 40−60°C). Colorless oil (453 mg, 50%). $[\alpha]_D^{r.t.}$ = −59, $[\alpha]_{578}^{r.t.}$ = −63, $[\alpha]_{546}^{r.t.}$ = −72, $[\alpha]_{436}^{r.t.}$ = −113 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR: δ = 0.68−1.70 (m, 13 H, C_6H_{11}, $CH_2C_6H_{11}$), 1.86 (br. s, 1 H, OH), 3.36 (m, 1 H, CHN), 3.48 (m, 2 H, CH_2OH), 6.88 (ddd, ^3J = 7.8, $^3J_{HP}$ = 4.5, ^4J = 1.1 Hz, 1 H, Ar-H^6), 7.20−7.34 (m, 11 H, H_{ar}), 7.42 (ddd, ^3J = 7.5, ^3J = 7.5, ^4J = 1.4 Hz, 1 H, H_{ar}), 7.78 (ddd, ^3J = 7.6, $^3J_{HP}$ = 4.0, ^4J = 1.4 Hz, 1 H, Ar-H^3), 8.57 (d, $^4J_{HP}$ = 3.9 Hz, 1 H, HC=N) ppm. ^{31}P{^{1}H} NMR: δ = −9.9 ppm. IR (KBr): $\tilde{\nu}$ = 3400 (ν_{O-H}), 1640 cm^{-1} ($\nu_{C=N}$). MS (PI-EI-MS, 70 eV): *m*/*z* (%) = 429 (15) [M], 352 (4) [M − C_6H_5], 316 (10) [$C_{21}H_{19}$PN], 288 (100) [$C_{17}H_{15}$PN], 212 (13), 183 (21) [$C_{12}H_8$P], 165 (13), 108 (17), 55 (14), 32 (14). $C_{28}H_{32}$ONP (429.54): calcd. C 78.29, H 7.51, N 3.26; found C 79.12, H 7.45, N 3.31.

(2*R*)-(−)-1-({1-[2-(Diphenylphosphanyl)phenyl]methylidene}amino)propan-2-ol (3): (*R*)-(−)-1-Aminopropan-2-ol (198 μL, 2.54 mmol) and (2-formylphenyl)diphenylphosphane (615 mg, 2.12 mmol) were used. Recrystallization was from petroleum ether (boiling range 40−60°C). Colorless solid (478 g, 54%), m.p. 58−60 °C. $[\alpha]_D^{r.t.}$ = −28, $[\alpha]_{578}^{r.t.}$ = −27, $[\alpha]_{546}^{r.t.}$ = −29, $[\alpha]_{436}^{r.t.}$ = −39 (*c* = 0.25, CH_2Cl_2). ^{1}H NMR: δ = 1.11 (d, ^3J = 6.3 Hz, 3 H, CH_3), 3.34 (ddd, ^2J = 12.3, ^3J = 8.2, ^4J = 1.4 Hz, 1 H, CH_2N), 3.60 (ddd, ^2J = 12.3, ^3J = 3.3, ^4J = 1.5 Hz, 1 H, CH_2N), 3.83 (dqd, ^3J = 8.2, ^3J = 6.3, ^3J = 3.3 Hz 1 H, C*H*OH), 6.89 (ddd, ^3J = 7.7, $^3J_{HP}$ = 4.5, ^4J = 1.3 Hz, 1 H, Ar-H^6), 7.22−7.35 (m, 11 H, H_{ar}), 7.42 (ddd, ^3J = 7.6, ^3J = 7.3, ^4J = 1.3 Hz, 1 H, H_{ar}), 7.81 (ddd, ^3J = 7.6, $^4J_{HP}$ = 3.8, ^4J = 1.5 Hz, 1 H, Ar-H^3), 8.72 (ddd, $^4J_{HP}$ = 3.9, ^4J = 1.5, ^4J = 1.4 Hz, 1 H, HC=N) ppm. ^{31}P{^{1}H} NMR: δ = −10.18 ppm. IR (KBr): $\tilde{\nu}$ = 3260 (ν_{O-H}), 1640 ($\nu_{C=N}$), 1450 cm^{-1} (ν_{P-H}). MS (PI-EI-MS, 70 eV): *m*/*z* (%) = 348 (23) [M], 303 (15) [M − HO − $CHCH_3$], 288 (100) [$C_{17}H_{15}$PN], 270 (40) [M − C_6H_5] 212 (21), 183 (31) [$C_{12}H_8$P], 165 (17), 134 (16), 197 (10); 43 (14). $C_{22}H_{22}$NOP (347.39): calcd. C 76.07, H 6.38, N 4.03; found C 75.82, H 6.33, N 4.05.

(S_h)-(−)- and (R_h)-(+)-MBA by Resolution of Racemic 5-(2′-Hex-3′-ynyl)-1-methylbarbituric Acid (MBA) with (−)-Brucine: MBA was prepared according to the literature.[9,10,12−14] For the optical resolution, racemic MBA (4.42 g, 19.9 mmol) was dissolved at room temperature in ethanol (50 mL) and added to a stirred solution of (−)-brucine (7.85 g, 19.9 mmol) in refluxing ethanol (30 mL). At room temperature a first fraction crystallized on standing. After 2 h, the colorless solid was filtered off and dried (fraction 1). Two other crops of the less soluble brucinium (S_h)-(−)-MBA salt were obtained after concentration, in somewhat smaller amounts (fractions 2 and 3). The combined fractions were recrystallized first from 60 mL of ethanol and then from 50 mL of ethanol. Colorless solid. Yield: 9.94 g, 81%, after two recrystallizations 5.58 g, 46%, m.p. 96−108 °C. $[\alpha]_D^{r.t.}$ = −55, $[\alpha]_{578}^{r.t.}$ = −58, $[\alpha]_{546}^{r.t.}$ = −70, $[\alpha]_{436}^{r.t.}$ = −143, $[\alpha]_{365}^{r.t.}$ = −308 (*c* = 0.3, $CHCl_3$). For ^{1}H NMR and IR of the brucinium (S_h)-(−)-MBA salt see ref.[13] (S_h)-(−)-MBA was liberated from a suspension of diastereomerically pure brucinium (S_h)-(−)-MBA salt (5.58 g, 9.00 mmol) in water (85 mL) by addition of HCl (32%, 2 mL). The precipitate was filtered off after 12 h of standing at 0 °C and recrystallized from ethanol. Colorless solid (940 mg, 42%), m.p. 108−110 °C. $[\alpha]_D^{r.t.}$ = −5.8, $[\alpha]_{578}^{r.t.}$ = −5.4, $[\alpha]_{546}^{r.t.}$ = −6.4, $[\alpha]_{436}^{r.t.}$ = −11.8, $[\alpha]_{365}^{r.t.}$ = −26.2 (*c* = 0.3, EtOH). Enantiomeric excess 98% (determined by GC). ^{1}H NMR and IR identical to those given in refs.[12,13] GC conditions: 25-m CP-Chirasil-Dex-CB column (coated with permethylated β-cyclodextrin, 0.25 mm inner diameter, 0.25 μm film thickness, from Chrompack), column temperature 165 °C, He pressure 1.2 bar, injector temperature 260 °C, detector temperature 260 °C, retention times: 26 min [(S_h)-(−)-MBA] and 28 min [(R_h)-(+)-MBA]. From the combined solutions of fractions 1−3 the diastereomerically pure brucinium (R_h)-(+)-MBA salt was obtained by crystallization

at −25 °C. Colorless solid (3.78 g, 30%), m.p. 107−119 °C. $[\alpha]_D^{r.t.}$ = −42, $[\alpha]_{578}^{r.t.}$ = −47, $[\alpha]_{546}^{r.t.}$ = −57, $[\alpha]_{436}^{r.t.}$ = −121, $[\alpha]_{365}^{r.t.}$ = −263 (c = 0.3, $CHCl_3$). ^1H NMR and IR data identical to those of the brucinium (S_h)-(−)-MBA salt. (R_h)-(+)-MBA was liberated from the diastereomerically pure brucinium (R_h)-(+)-MBA salt (3.78 g, 6.31 mmol) and recrystallized from ethanol. Colorless solid (550 mg, 23 °C), m.p. 105−107 °C. $[\alpha]_D^{r.t.}$ = 5.7, $[\alpha]_{578}^{r.t.}$ = 5.7, $[\alpha]_{546}^{r.t.}$ = 6.7, $[\alpha]_{436}^{r.t.}$ = 11.0, $[\alpha]_{365}^{r.t.}$ = 19.0 (c = 0.3, EtOH). Enantiomeric excess 98% (determined by GC).

Synthesis of Methohexital by Enantioselective Palladium-Catalyzed Allylation of MBA: MBA, (S_h)-(−)-MBA, or (R_h)-(+)-MBA (500 mg, 2.25 mmol) and triethylamine (329 μL, 2.39 mmol) were dissolved in dichloromethane/toluene (1:1, 11.7 mL) at 38 °C under nitrogen. After 2 min, a solution of [Pd(acac)$_2$] (6.85 mg, $2.25\cdot10^{-2}$ mmol) and a phosphaneimine ligand ($9.00\cdot10^{-2}$ mmol) in dichloromethane/toluene (1:1, 11.7 mL) was added, and the catalysis was started with allyl acetate (169 μL, 2.50 mmol). The solution was stirred at 38 °C for 72 h. For workup the reaction mixture was washed with HCl (0.2 M, 25 mL). The organic layer was dried with Na_2SO_4. The solid was filtered off and washed with dichloromethane (total of 30 mL). Removal of the solvent gave an oily, yellowish residue, which was chromatographed on silica gel with dichloromethane/acetonitrile (25:1). After elution of a reddish fraction (decomposed ligand and excess of allyl acetate), various (7−15) 10-ml portions containing the product were collected. The purity was checked by TLC (silica 60, Merck; dichloromethane/acetonitrile, 25:1). The first fraction was contaminated with allyl acetate and discarded; the others were combined. After complete elution of methohexital, unchanged MBA was eluted by changing the solvent to dichloromethane/acetonitrile (3:1). Methohexital was obtained as a colorless oil, which crystallized at room temperature after several days. The yields of methohexital (and MBA) were determined by weighing. Methohexital: colorless solid (maximum yield 557 mg, 94%), m.p. 58−62 °C. For ^1H NMR, IR and MS see refs.[12,13] GC conditions: 30-m Chiraldex B-PM column (coated with permethylated β-cyclodextrin, 0.25 mm inner diameter, from ASTEC), column temperature 125 °C, H_2 pressure 1.75 bar, injector temperature 260 °C, detector temperature 260 °C, retention times: 146 min (R_bR_h), 150 min (R_bS_h), 159 min (S_bS_h), 177 min (S_bR_h).

X-ray Crystal Structure Determination of (S_bR_h)-Methohexital: Data collection was performed with an Enraf−Nonius CAD-4 diffractometer. All data were corrected for Lorentz and polarization effects. Final unit cell parameters were obtained by least-squares refinement on a set of 25 reflections in a Θ-range between 10.65 and 38.45°. The structure was solved with direct methods (SIR-97)[24] and subsequent difference Fourier methods. Refinement on F^2 was carried out by full-matrix, least-squares techniques (SHELXL-97).[25] All non-H atoms were refined with anisotropic thermal parameters. H atoms were located from difference Fourier syntheses and refined with isotropic thermal parameters in two different ways: all as riding atoms with $U_{iso}(H) = 1.2U_{eq}(C)$ apart from the N-bonded hydrogen atom, which was free. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-158458. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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