289. Relationship between Molecular Properties and Conformation of Chiral Alkanes

by Ugo Azzena, Pier Luigi Luisi[1]), Ulrich W. Suter

Technisch-Chemisches Labor der ETH, Zurich, Switzerland

and Serafino Gladiali

Istituto di Chimica Applicata, Università di Sassari, Italy

(9.IX.81)

Summary

Mixtures of the diastereomers of 2,2,3,5,6-pentamethylheptane were prepared in two ways, either starting with compounds of (3R)-configuration, or from compounds of (5R)-configuration. Comparison of the GC. and optical rotatory power of the fractions of these two mixtures permitted the unambiguous assignment of the absolute configuration and molar rotatory power to the various diastereomers ($[M]_D^{25} = +119.1°$ for the (3R,5R)- and $[M]_D^{25} = +79.8°$ for the (3R,5S)-diastereomer). The very high molar rotatory power which was expected on the basis of the conformational analysis carried out with a rotational-isomeric-3-states model is interpreted as arising from the molecular 'conformational rigidity', i.e. from the presence of only few conformers. Conformational properties of these compounds were computed using a new approach, which scans the whole space of each bond (2π) in 5° steps and calculates the conformational energy based upon semiempirical potential functions. The conformational flexibility of each bond of the two diastereomers is evaluated in terms of the a priori probability density function of that bond. This allows us to analyze in detail how configurational differences affect conformational properties. The molar rotatory power of the two diastereomers as calculated with a new method recently developed in our group is in excellent agreement with experimental data. The molar rotatory power is analyzed in terms of the contribution of the single bonds.

Introduction. – The conformational equilibrium of open chain molecules in solution or liquid state is usually characterized by the rapid interconversion of many conformers (or rotational isomers of the molecule). The actual number of conformers to be taken into account depends on ones definition of rotamer (or bond rotational isomer). Quite often, in the rotational-isomeric-state approximation

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[1]) To whom correspondance should be addressed.

[1–3], only three states are considered for each bond (the so called *trans* (antiperiplanar), *gauche*$^+$ and *gauche*$^-$ (synclinal), indicated as *t*, *g*$^+$ and *g*$^-$) so that the number of rotational isomers for the molecules is 3^n, where *n* is the number of bonds around which rotation is considered. This yields large numbers even with *n* 4–5; however, in some cases the conformational equilibrium is overwhelmingly shifted towards a small number of conformations. These molecules are commonly referred to as 'conformationally rigid' [4–9], a term which should not be taken literally [9]. The study of conformationally rigid compounds is particularly interesting. One would like to understand which factors govern the rigidity and which physical properties are more directly affected by this particular conformational situation. It has been shown, for example, that isotactic poly-*a*-olefins containing an asymmetric C-atom in *a*- or *β*-position with respect to the main chain are characterized by extremely large optical rotations. This has been ascribed to the conformational rigidity of the monomer unit, and in order to demonstrate this, two chiral low molecular weight open chain paraffins were synthesized [5] in which the conformational equilibrium was expected to reflect that of the monomer unit of isotactic poly-3-methyl-1-pentene in either the right- or the left-handed spiral conformations. Indeed, large optical activities of opposite sign were found for these low molecular weight paraffins [5], showing that the elevated optical rotation in polymers was due to local conformational effects, and not to phenomena arising from chromophore interactions in the polymer chain (as in the case of poly-*a*-amino acids).

The optical activity of **1a** and **1b** (see *Scheme 1*) was the highest ever found for open chain paraffins, and this brought up the question of whether and to what

Scheme 1. Fisher *projections of* **2a** *and* **2b** *and of the parent compounds* **1a** *and* **1b**
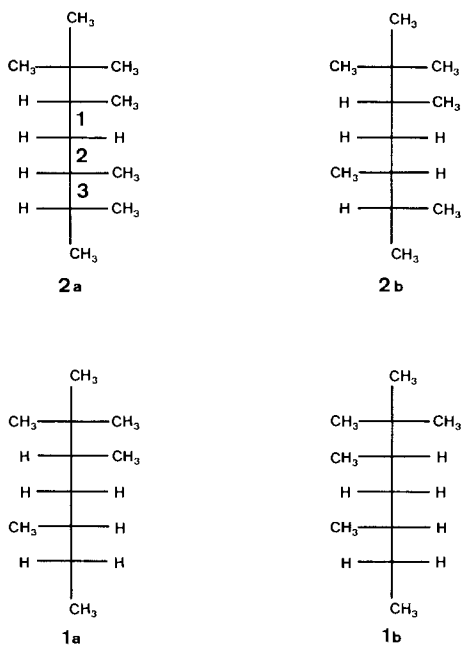
extent parent compounds are also endowed with such exceptional optical rotations. In this paper, we will deal with this question and present the synthesis of the diastereomers **2a** and **2b** (see *Scheme 1*) which, according to the 3-state-rotational scheme [5], are provided with a very high degree of conformational rigidity and high optical rotation. The study of rigid compounds of this sort is made more timely by the appearance of a method to examine the conformational flexibility of single bonds in terms of *a priori* probability density [10]. This allows a comparison of the relative conformational flexibilities of the individual bonds in a paraffin molecule. Also, in that paper, the optical rotation was calculated for the whole paraffin molecule as well as for the individual bonds [10]. In the present paper, such an analysis will be carried out for the two new compounds **2a** and **2b**, and the results will be compared with those of the parent compounds **1a** and **1b**. This study shows how relatively modest changes in chemical structure and configuration might affect changes in conformational equilibrium. as well as changes in optical rotation.

Results and discussion. – The mixture **2a/2b** of the diastereomers of 2,2,3,5,6-pentamethylheptane *with (3R)-configuration* was prepared by the sequence $3 \rightarrow 4 \rightarrow 5 \rightarrow 6 \rightarrow 7 \rightarrow 8$ the key intermediate being $(+)$-(R)-3,4,4-trimethylpentanoic acid $((+)$-(R)-**5**) [15] of 92.5% optical purity *(Scheme 2)*. It was possible to determine the composition of the mixture **2a/2b** by GC. on a high resolution capillary column. A partial separation of the diastereoisomers was obtained by fractional distillation through a spinning band column *(Table 1)*. From the composition and the optical activity of the different fractions, corrected to 100% optical purity, and by assuming complete retention of configuration throughout the sequence $(+)$-(R)-**5** $\rightarrow$ $\rightarrow$ **2a/2b**, $[M]_D^{25} = +119.1°$ (neat) was calculated for the diastereoisomer **2b** with the lower GC. retention time, and $[M]_D^{25} = +79.8°$ (neat) for the diastereoisomer **2a** with the higher GC. retention time *(Table 2)*. For the assignment of the absolute configuration, another mixture of two diastereoisomers of 2,2,3,5,6-pentamethylheptane *with (5R)-configuration* was prepared from $(+)$-(S)-2,3-dimethyl-1-chlorobutane (**9**) [15] of 9.8% optical purity *via* the
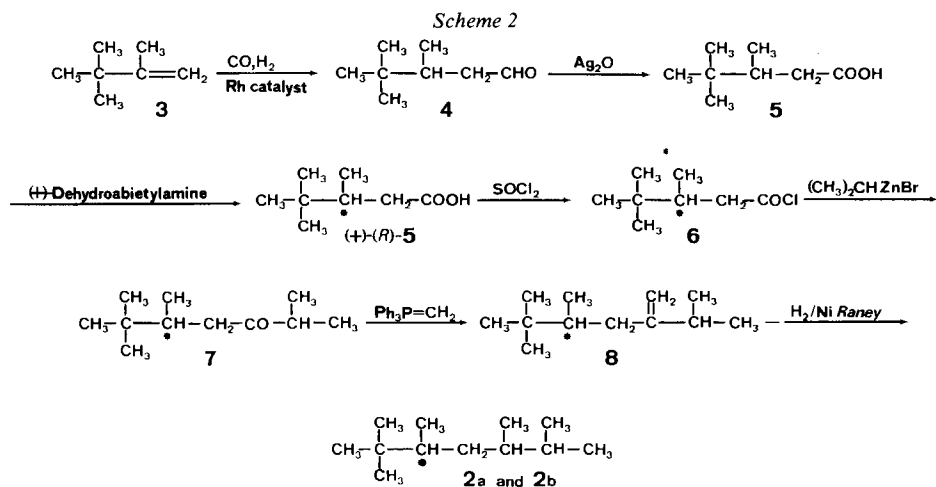
Scheme 2

Table 1. *Optical rotation of fractions containing* **2a** *and* **2b** *in different ratios*[a])

B.p. at 30 Torr	2b[b]) [%]	2a[c]) [%]	α_D^{25} (neat; $l = 0,1$)
79–80°	86 ± 2	14 ± 2	$+4.72°$
80°	77 ± 2	23 ± 2	$+4.59°$
80–81°	58 ± 2	42 ± 2	$+4.25°$

[a])   As measured by GLC.: 50 m *Apiezon L* capillary column.
[b])   Component with the lower retention time.
[c])   Component with the higher retention time.

intermediates **10** and **11** *(Scheme 3)*. This mixture which, according to GC. contained $55 \pm 2\%$ of the diastereomer **2b**, showed $\alpha_D^{25} = +0.13°$ (neat; $l = 0.1$). In this mixture the two diastereomers $(3R, 5R)$ and $(3S, 5R)$ must have opposite optical rotations, and, in particular, the $(3R, 5R)$ isomer **2b** must have a positive rotation (s. above). Therefore, the configuration $(3R, 5R)$ has to be assigned to the diastereomer **2b** with $[M]_D^{25} = +119.1°$, and the configuration $(3R, 5S)$ to the diastereomer **2a** with $[M]_D^{25} = +79.8°$ (see *Scheme 1* and *Table 2*).

The molar rotation of the two diastereomers is very high and comparable in absolute value to that of the two 'conformationally rigid' paraffins synthesized earlier [5]. *Scheme 1* and *Table 2* offer a comparison of the structures and of the molar rotations at the sodium-D-line. As in the case of compounds **1a** and **1b**, the very high optical activity of **2a** and **2b** can be ascribed to the position of the conformational equilibrium. According to *Brewster*'s original approach [11], the conformational analysis can be described in terms of the rotation around three C, C-bonds only (which in *Scheme 1* are indicated with the numbers 1, 2, 3 for compound **2a**). For **2a** only one molecular conformation would be allowed, namely t_1, g_2^+, t_3, whereas two conformations (t_1, t_2, g_3^+ and t_1, t_2, g_3^-) are allowed for **2b**. Analogously, for **1a** and **1b** the first-order-approximation approach gave one and two allowed conformations, respectively [5]. Notice that according to the 3-state-rotational-isomeric scheme, the total number of possible conformations for a paraffin of this type is $3^3 = 27$. Therefore, all the compounds of *Table 2* have to be considered as highly hindered from the conformational point of view, or, as is commonly said, somewhat improperly, 'conformationally rigid'. This conformational situation generally brings about a high optical activity, due to the lack of a sufficient degree of compensation.

The progress recently made in the conformational analysis of low and high molecular weight paraffins [3] [10] [12] [13] permits us to draw a much more detailed
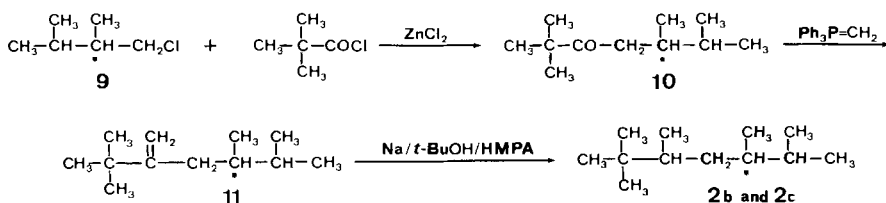
Scheme 3

Table 2. *Optical rotatory properties of conformationally rigid paraffins* (at the sodium-D line), in degrees cm^{2}dmol^{-1}

Compound	$[\Delta M_1]^{a)}$	$[\Delta M_2]^{a)}$	$[\Delta M_3]^{a)}$	$[M]_D^{b)}$	$[M]_D^{c)}$
(3R,5S)-2,2,3,5,6-pentamethylheptane (2a)	+ 43.2	− 31.8	+ 68.4	+ 79.9	+ 79.8
(3R,5R)-2,2,3,5,5-pentamethylheptane (2b)	+ 69.9	+ 57.2	+ 2.7	+ 129.8	+ 119.1
(3R,5S)-2,2,3,5-tetramethylheptane (1a)$^{d)}$	+ 60.1	+ 57.7	+ 25.0	+ 142.8	+ 137.8
(3S,5S)-2,2,3,5-tetramethylheptane (1b)$^{d)}$	− 58.4	− 43.4	− 15.6	− 117	− 97.5

a) Contribution of bond i to the total molar optical rotation, calculated at 300 K. The numbers refer to the position of the bond, as indicated in *Scheme 1*.
b) Total molar optical rotation, calculated at 300 K.
c) Experimental molar optical rotation.
d) Data from [5].

picture of the conformational properties of the compounds **1** and **2**. Also the methods for calculating optical activity have been considerably improved [10] [14]. An accurate relationship between chemical structure, conformational equilibrium and optical activity can therefore be assessed. In the following, we describe this detailed situation for **2a** and **2b**, and compare it with the one of the parent compounds **1a** and **1b**, described earlier [5] [6] [10].

Usually, bond conformations of a molecule are described by an energy map. However, this method is not practical for molecules having more than two bonds. An alternative method has been suggested recently [10]. This is based upon the graphical representation of the *a priori* probability density function ψ_i for each torsion angle φ_i as given in the *Equation*, Z being the conformational partition

$$\psi_i = \psi_i(\varphi') = Z^{-1} \int \exp(-E^*(\underline{\varphi})/RT) \prod_{j \neq i} \pi \, d\varphi_j$$
$$\{\varphi\} \mid \varphi_i = \varphi'$$

function and E^* the relative energy of a given conformation. The vector φ is composed of φ_i for the bond i, *i.e.* φ $(\varphi_1, \varphi_2 \cdots \varphi_n)$, and $\{\varphi\}$ denotes the entire accessible φ space. According to *Eqn.* each bond will be represented by probability curves (see *Fig. 1*), whose sum integral is normalized to unity. Thus, a bond which exists only in one conformation will be represented by a single peak (see for example φ_1 and φ_2 of *Fig. 1b*), and the narrower the peak is, the more 'rigid' is the molecule around this bond. Note that the bond's φ_1 and φ_2 of **2b** *(Fig. 1b)* are close to the *trans*-position, but these torsion angles are shifted more towards negative φ values (anticlockwise). Moreover, the probability density is spread over a large interval in the case of φ_1 (from − 40 to + 20° *ca.*) which is smaller in the case of φ_2. Finally, φ_3 three ranges of existence, differing in surface areas (*i.e.* in relative probability).

The change of configuration at C(3) (*i.e.* going from **2b** to **2a**) brings about significant changes in the conformational properties. Infact, in the case of **2a** φ_3 belongs to the most rigid bond (around a *trans* position), whereas φ_1 and φ_2 are associated with a much larger conformational flexibility. They are also populated around 0°, but φ_1 has a considerable secondary maximum at *ca.* + 40°, and φ_2 at *ca.* − 80°. More details about the relationship configuration/conformation can be gath-
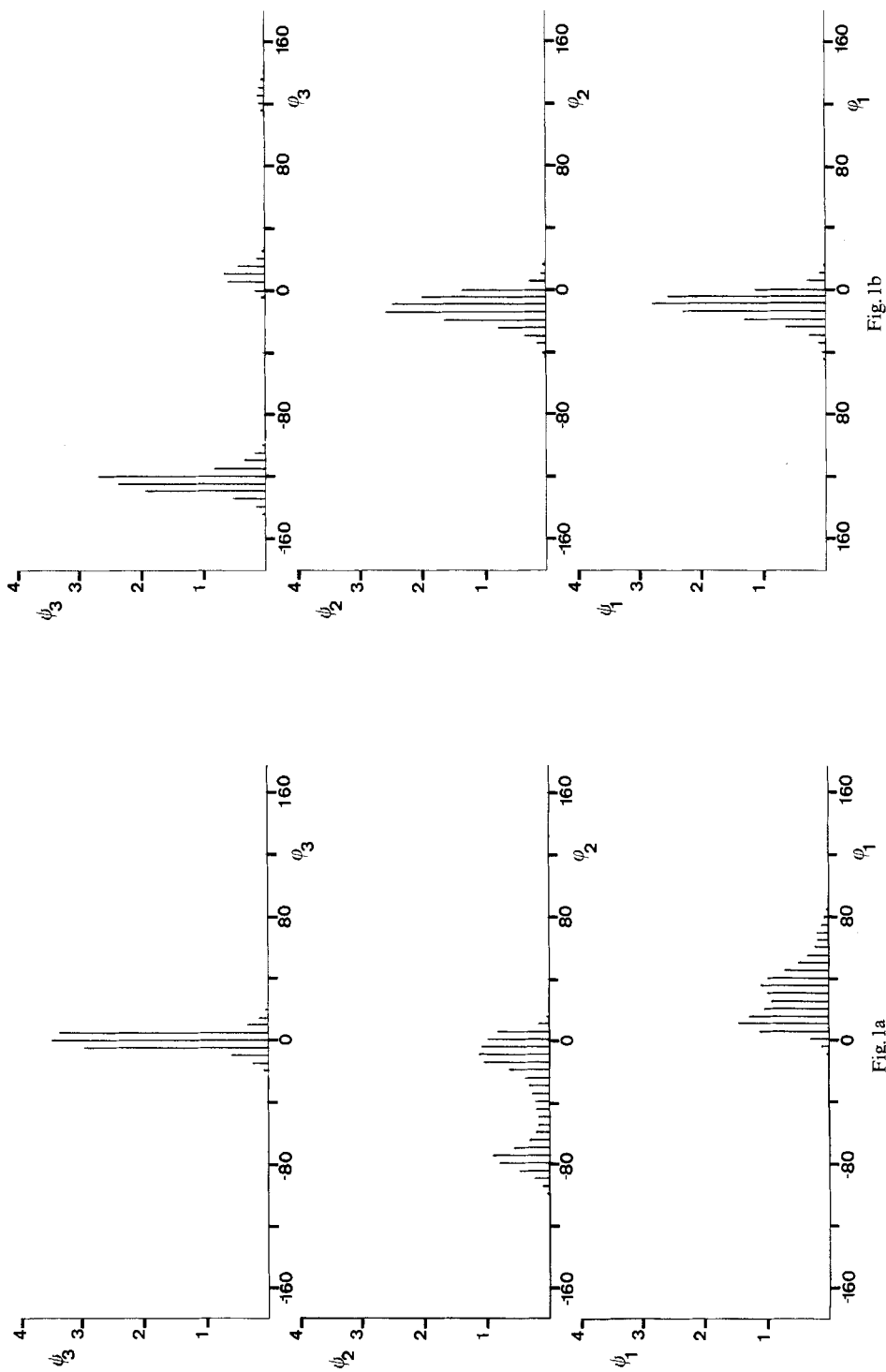
Figure. *Computed at 300 K. A priori probability density functions of the torsion angles for a)* (3R, 5S)- *2,2,3,5,6-pentamethylheptane* (**2a**) *and b)* (3R,5R)-*2,2,3,5,6-pentamethylheptane* (**2b**)

Fig. 1a

Fig. 1b

ered from the comparison with the bond flexibility of the two parent compounds **1a** and **1b** presented earlier [10]. In the previous papers [9] [10] we have also discussed the conformational properties of different molecules in terms of the function $F_s = Z^{1/n}$ 2π, n being the number of bonds around which rotation is considered, and Z being the conformational partition function of the molecule. The function F_s, which can vary between 0 and 1, expresses the fraction of conformational space accessible in average to a bond of the molecule, and permits a comparison among different molecules in terms of average flexibility. It was shown before [10] that the flexibility number of paraffins such as the unbranched pentane or the monosubstituted methylpentane was around 10–13%, whereas F_s for 'conformationally rigid' alkanes, such as **1a** and **1b** was around 7–8% [10]. Here we obtained $F_s = 7.7\%$ for **2a** and $F_s = 6.9\%$ for **2b**. Calculation of optical rotation according to the procedure outlined in the previous paper [10], based on the continuumscheme described above, yielded the results presented in *Table 2*. The good agreement between calculation and experiment can be taken as an indication of the reliability of the conformational scheme employed. The procedure also gives the contributions of individual bonds to the total optical rotation [10], and these values are also included in *Table 2*. The relationship between these [ΔM_i] and the local conformation is discussed in the previous paper [10].

Experimental Part

General remarks. Solvents were dried and distilled shortly before use. Commercial reagents were used without purification. 2,3,3-Trimethyl-1-butene (**3**) was prepared as described in [16], and (+)-(*S*)-2,3-dimethyl-1-chlorobutane (**9**) with 9.8% optical purity as described in [15]. Boiling points are not corrected. Optical rotations were taken on a *Perkin-Elmer* 141 polarimeter. NMR. spectra were taken at 90 MHz in CDCl₃ with TMS as an internal standard using a *Bruker* WH 90 *Fourier* transform spectrometer by Mr. *F. Bangerter;* abbreviations: s = singlet, d = doublet, m = multiplet, br. = broad. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. Mass spectra were recorded on a *Hitachi-Perkin-Elmer* RMU-6L at 70 eV by Dr. *A. Stefani.*

*Synthesis of 3,4,4-trimethylpentanal (**4**).* A solution of **3** (17.6 g, 0.18 mol) in benzene (60 ml) and triethylamine (7.5 ml) was hydroformylated for 24 h in a rocking steel autoclave at 100 atm pressure (CO/H₂ 1:1), in the presence of ClRh(CO)[P(Ph)₃]₃ (0.15 g, 1.5 · 10⁻⁴ mol). *Via* the hydrogensulfite adduct, **4**, b.p. 60°/30 Torr, was obtained in 90% yield ([17]: b.p. 64–67°/31 Torr). – ¹H-NMR.: 0.87 (*s*, 3 H₃C–C(4)); 0.93 (*d*, *J* = 7, H₃C–C(3)); 1.80–2.45 (br., 1 H–C(3) and 2 H–C(2)); 9.6 (*s*, CHO).

*Synthesis of 3,4,4-trimethylpentanoic acid (**5**).* To a suspension of Ag₂O (43.5 g) in 300 ml of 1.2M aq. NaOH **4** (24 g, 0.19 mol) was added dropwise. After 3 h stirring at room temp., the mixture was filtered, acidified with conc. sulfuric acid and extracted with ether. The ethereal solution was dried over Na₂SO₄, the solvent evaporated and the residue vacuum distilled to give **5** (20.25 g, 74%), b.p. 90°/4 Torr ([15]: b.p. 126°/18 Torr). – ¹H-NMR.: 0.88 (*s*, 3 H₃C–C(4)); 0.92 (*d*, *J* = 7, H₃C–C(3)); 1.85–2.55 (br., 1 H–C(3) and 2 H–C(2)); 11.98 (*s*, COOH). – ¹³C-NMR.: 15 (CH₃–C(3)); 27.1 (3 CH₃–C(4)); 32.7 (C(4)); 37.5 (C(2)); 39.9 (C(3)); 181.2 (C(1)). – MS.: 144 (*M*⁺).

*Isolation of (+)-(R)-**5**.* Under stirring **5** (139.5 g, 0.97 mol) was added to a solution of (+)-dehydro-abietylamine (276.5 g, 0.97 mol) in ether (2 l) giving 400 g of salt. After 3 crystallizations of the latter from absolute ethanol/chloroform 45 g of salt were obtained, m.p. 149–151°, $[\alpha]_D^{25} = +31.8°$ ($c \approx 2$, CHCl₃). This was dissolved in a cold NaOH-solution, and the dehydroabietylamine extracted with ether. From the acidification of the aqueous solution and extraction with ether. (+)-(*R*)-**5** (11 g, 7.8%), $[\alpha]_D^{25} = +19.05°$ ($c \approx 2.5$, EtOH), optical purity 92.5%, was recovered ([15]: $[\alpha]_{D\,max}^{25} = +20.6°$ ($c \approx 2.5$, EtOH)).

*Synthesis of (R)-3,4,4-trimethylpentanoyl chlorid (**6**).* To (+)-(*R*)-**5** (11 g, 0.076 mol) thionyl chlorid (18 g, 0.15 mol) was added dropwise. The mixture was then heated at 80° for 5 h. The unreacted thionyl chlorid was then evaporated and the residue vacuum distilled to give **6** (10.85 g, 85%), b.p. 85°/30 Torr.

Synthesis of (+)-(R)-2,5,6-tetramethyl-3-heptanone (**7**). A solution of **6** (10.85 g, 0.064 mol) in benzene (30 ml) was added under N_2 to a freshly prepared suspension of isopropyl zinc bromide (0.09 mol) in benzene; the resulting mixture was stirred at room temp. overnight. Excess dil. hydrochloric acid was added, the organic layer separated, washed with sat. $NaHCO_3$-solution, water and then dried over Na_2SO_4. Evaporation and vacuum distillation gave **7** (8.35 g, 75%), $a_D^{25} = +19.3°$ (neat, $l= 1$), b.p. 100°/30 Torr. – ^{1}H-NMR.: 0.75 (d, $J=7$, H_3C–C(5)); 0.88 (s, 3 H_3C–C(6)); 1.08 (d, $J=7$, 2 H_3C–C(2)); 1.85 (m, 1 H–C(5)); 2.25 (d, $J=10$, 2 H–C(4)); 2.55 (m, 1 H–C(2)). – ^{13}C-NMR.: 15.3 (CH_3–C(5)); 18.2 and 18.4 (2 CH_3–C(2)); 27.3 (3 CH_3–C(6)); 32.6 (C(6)); 38.3 (C(5)); 41.1 (C(2)); 43.5 (C(4)); 214 (C(3)). – MS.: 170 (M^+).

Synthesis of (+)-(R)-2-isopropyl-4,5,5-trimethyl-1-hexene (**8**). A solution of **7** (8.35 g, 0.05 mol) in dimethylsulfoxide (25 ml) was rapidly added, under N_2, to a solution of methylidenetriphenyl-phosphorane (0.12 mol) in dimethylsulfoxide (25 ml) [18], and the mixture was stirred at 60° overnight. An equal amount of water was added, and the mixture was steam distilled. The organic layer was separated and the aqueous phase extracted with ether. The organic fractions were dried over Na_2SO_4, evaporated, and vacuum distilled: **8** (4.88 g, 58%), b.p. 81°/30 Torr, $a_D^{25} = +2.37°$ (neat, $l= 1$). – ^{1}H-NMR.: 0.74 (d, $J=7$, H_3C–C(4)); 0.87 (s, 3 H_3C–C(5)); 1.0 (d, $J=3$, CH_3CHCH_3); 1.1 (d, $J=3$, CH_3CHCH_3); 1.2–2.4 (br., 1 H–C(4), 2 H–C(3) and CH_3CHCH_3); 4.65 (m, 1 H–C(1)); 4.75 (m, 1 H–C(1)). – ^{13}C-NMR.: 13.9 (CH_3–C(5)); 21.7 (CH_3CHCH_3); 22.5 (CH_3CHCH_3); 27.5 (CH_3–C(4)); 32.8 (C(3)); 33 (C(5)); 38 (C(4)); 41.1 (CH_3CHCH_3); 107.8 (C(1)); 155.2 (C(2)). – MS.: 168 (M^+).

Synthesis of (3R,5S)- and (3R,5R)-2,2,3,5,6-pentamethylheptane (**2a** and **2b**). A solution of **8** (4.88 g, 0.029 mol) in absolute ethanol (50 ml) was hydrogenated for 24 h in a rocking steel autoclave at 100 atm H_2 in the presence of a suspension of *Raney* nickel in absolute ethanol (25 ml). Then, the mixture was filtered and the solvent evaporated. The crude **2a/2b** was analyzed by GC. (50 m *Apiezon L* capillary column): $72\pm2\%$ of **2b** (lower retention time), and $28\pm2\%$ of **2a** (higher retention time). – MS.: 170 (M^+) and a closely equal fragmentation for both components.

The mixture **2a/2b** was vacuum distilled through a spinning band column, and three fractions with different diastereoisomeric compositions were collected *(Table 1)*, b.p. 79–81°/30 Torr. A racemic sample prepared in the same way showed $d_4^{25} = 0.76505$ ([19]: b.p. 188.8°/750 Torr for a racemic sample).

Synthesis of (+)-(R)-2,2,5,6-tetramethyl-3-heptanone (**10**). An ethereal solution of the freshly prepared *Grignard* derivative of (+)-(S)-**9** (0.023 mol), 9.8% optical purity [16], was added dropwise, under N_2, to a well stirred mixture of anhydrous $ZnCl_2$ (3.13 g, 0.023 mol) in ether (10 ml). After the initial reaction had subsided, the mixture was boiled for 3 h, during which time about all ether was distilled away and replaced with an equal amount of benzene. A solution of 2,2-dimethylpropanoyl chloride (2.75 g, 0.023 mol) in benzene (10 ml) was then added; the resulting mixture was stirred over-night at room temp. and then treated in the usual manner to give **10** (3 g, 74%), $a_D^{25} = +2.54°$ (neat, $l= 1$), b.p. 68°/30 Torr. – ^{1}H-NMR.: 0.78, 0.83 and 0.87 (3 d, $J=6.5$, 2 H_3C–C(6) and H_3C–C(5)); 1,1 (s., 3 H_3C–C(2)); 1.4–2.1 (br., 1 H–C(5) and 1 H–C(6)); 2.35 (d, $J=7$, 2 H–C(4)). – ^{13}C-NMR.: 15.8, 18.3 and 19.9 (2 CH_3–C(6) and CH_3–C(5)); 26.3 (3 CH_3–C(2)); 32 and 33.9 (C(5) and C(6)); 40.9 (C(4)); 44.2 (C(2)); 215.3 (C(3)). – MS.: 170 (M^+).

Synthesis of (+)-(R)-2-t-butyl-4,5-dimethyl-1-hexene (**11**). A solution of **10** (3 g, 0.017 mol) in dimethylsulfoxide (15 ml) was rapidly added, under N_2, to a well stirred freshly prepared solution of methylidenetriphenylphosphorane [18] (0.047 mol) in dimethylsulfoxide (15 ml). The mixture was stirred overnight at 60° and then treated in the usual way to obtain **11** (1.68 g, 58%, $a_D^{25} = +2.45°$ (neat, $l= 1$), b.p. 60°/30 Torr. – ^{1}H-NMR.: 0.75, 0.81 and 0.86 (3 d, $J=7$, 2 H_3C–C(5) and H_3C–C(4)); 1.05 (s, $(CH_3)_3C$); 1.4–2.4 (br., 2 H–C(3), 1 H–C(4) and 1 H–C(5)); 4.7 (m, 1 H–C(1)); 4.9 (m, 1 H–C(1)). – ^{13}C-NMR.: 15, 17.8 and 20.5 (2 CH_3–C(5) and CH_3–C(4)); 26.4 (($CH_3)_3C$); 29.5 (($CH_3)_3C$); 32 (C(3)); 36.3 and 37.1 (C(4) and C(5)); 106.9 (C(1)); 156.1 (C(2)). – MS.: 168 (M^+).

Synthesis of (3R,5R)- and (3S,5R)-2,2,3,5,6-pentamethylheptane (**2b** and **2c**). According to a general procedure in [20] **11** (1.56 g, 0.0093 mol) was reduced to **2b/2c** with sodium/t-BuOH in hexamethyl-phosphoric triamide in 75% yield, b.p. 80°/30 Torr, $a_D^{25} = +0.13°$ (neat, $l=0.1$). The mixture was analysed by GC. (50 m *Apiezon L* capillary column): $55\pm2\%$ of **2b** (lower retention time), and $45\pm2\%$ of **2c** (higher retention time).

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