

133. Conformation and Dynamics of (–)- β -Caryophyllene

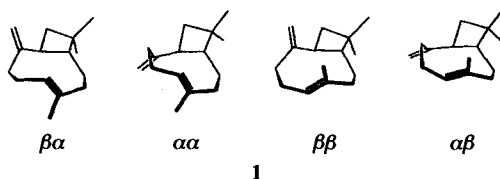
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(–)- β -Caryophyllene (**1**) adopts three conformations in solution: $\alpha\alpha$ (48%), $\beta\alpha$ (28%), and $\beta\beta$ (24%). The conformations were identified by an analysis of the ^{13}C - and ^1H -NMR spectra at -87.2 and -153.8° in connection with APT, HETCOR, and COSY spectra, and subsequent NOESY experiments. The activation parameters of the conversion $\alpha\alpha \rightarrow \beta\alpha$ were determined from a bandshape analysis of exchange-broadened ^{13}C -NMR spectra of 8-[methylene- ^{13}C]-**1** to give $\Delta H^\ddagger = 5.9 \pm 0.3$ kcal/mol, $\Delta S^\ddagger = -8.1 \pm 1.8$ cal/mol \cdot K, and $\Delta G_{298}^\ddagger = 8.3 \pm 0.8$ kcal/mol. The observed population ratio of the different conformers is best described by MM3.

1. Introduction. – (–)- β -Caryophyllene (**1**) is one of the most widespread sesquiterpenes and has been proposed as biogenetic precursor of several other sesquiterpenes, thought to be formed *via* rearrangement routes including transannular cyclizations [1]. Indeed, sulfuric-acid-catalyzed rearrangement yields a plethora of products including several natural sesquiterpenes [2]. Mechanistically, the product formation has been explained by an initial protonation of the exocyclic double bond of conformation $\beta\alpha$, and the endocyclic double bond of conformations $\alpha\alpha$ and $\beta\beta$, respectively [2]. However, albeit evidence for an equilibrium between a total of three conformers exists [3], a conclusive assignment considering the four possible conformers $\beta\alpha$, $\alpha\alpha$, $\beta\beta$, and $\alpha\beta$ is missing.



In the past, two important studies on the conformation and dynamics of (–)- β -caryophyllene (**1**) have been performed. In both cases, the conformational assignment was based on force-field calculations (*Table 1*). In 1981 [4], a ^{13}C -NMR high-temperature study indicated the existence of two conformers. At $+35^\circ$, their ratio was 76:24 and the corresponding barrier of inversion amounted to $\Delta G_{308}^\ddagger = 16.25$ kcal/mol. According to calculations with MM1 [4], these conformers were $\beta\alpha$ (75%) and $\beta\beta$ (21%), the population of two other conformers, $\alpha\alpha$ (3%) and $\alpha\beta$ ($< 1\%$), being too low. In 1989 [3], a third conformer was detected: A low-temperature ^{13}C -NMR study revealed that the major conformer observed at $+35^\circ$ was in fact a 1:1 mixture of two rapidly interconverting conformers with an inversion barrier of $\Delta G_{308}^\ddagger = 8.8$ kcal/mol. This time, the assignment proved troublesome as the results from both MM1 [4] and MM2 [3] were conflict-

Table 1. Heats of Formation and Population of the Different Conformers of (–)- β -Caryophyllene (**1**) at 298 K As Determined by Force-Field Calculations Using MM1, MM2, and MM3

	ΔH_f [kcal/mol] (%)			
	$\beta\alpha$	$\alpha\alpha$	$\beta\beta$	$\alpha\beta$
MM1	12.94 (75)	14.78 (3)	13.69 (21)	16.94
MM2	12.63 (39)	14.17 (3)	12.40 (58)	17.25
MM3	18.54 (29)	18.23 (44)	18.56 (26)	23.19

ing: MM1 favored $\beta\alpha$ (75%) over $\beta\beta$ (21%) and $\alpha\alpha$ (3%), while MM2 favored $\beta\beta$ (58%) over $\beta\alpha$ (39%) and $\alpha\alpha$ (3%). However, as in both cases $\alpha\alpha$ was the only remaining conformer that was populated to a certain extent, the choice of $\alpha\alpha$ as third conformer and $\beta\alpha$ as exchanging partner was obvious. For this pair, the observed low barrier of inversion was to be expected and in fact could be reproduced. Using the torsional angle driver option of MM2, the calculated barrier amounted to $\Delta H_f^\ddagger = 8.1$ kcal/mol [3].

The only attempt for a spectroscopic assignment delivered an erroneous result: In 1994 [5], a NOESY experiment at -40° was misinterpreted such, that the major component at $+35^\circ$ was attributed to a pure $\beta\alpha$ conformation, albeit the NOEs reported could also account for an $\alpha\alpha$ conformation or a mixture of both. Taking into account that a recent calculation using MM3 [2] favors $\alpha\alpha$ (44%) over $\beta\alpha$ (29%) and $\beta\beta$ (26%), the situation is confusing: The results from MM1, MM2, and MM3 are contradictory (Table 1), and no direct evidence for the identity of any of the three conformers detected exists. We, therefore, investigated the conformation and dynamics of **1** anew.

Our general proceeding was as follows: we first assigned all ^1H - and ^{13}C -NMR signals of the two components present at -87.2° , then performed a NOESY experiment at this temperature and thereby identified the minor component as $\beta\beta$ conformation. We then repeated the procedure for the three components present at -153.8° and identified the two remaining components as $\alpha\alpha$ and $\beta\alpha$ conformation. Finally, we determined the complete set of activation parameters for the conversion of $\alpha\alpha$ to $\beta\alpha$ via a bandshape analysis of ^{13}C -labelled (–)- β -caryophyllene (**1**). In the following, we detail our methods and results.

2. Results. – 2.1. *General.* To study the conformational behavior of **1**, we first recorded ^1H - and ^{13}C -NMR spectra at $+25.0$, -87.2 , -108.0 , -129.8 , -141.6 , and -153.8° and, thereby, confirmed that the resonance set of the major component observed at -87.2° split off when the temperature went down while the minor component persisted (Fig. 1). Integration of the signals of the exocyclic methylene groups yielded an averaged ratio (^1H , ^{13}C) of 76:24 for the two components present at -87.2° , and 48:28:24 for the three components present at -153.8° .

2.2. *Identification of the $\beta\beta$ Conformer.* Unfortunately, a direct assignment of the three components present at -153.8° proved hardly feasible, because two of the three signal sets had similar intensities. Therefore, we first analyzed the spectra at -87.2° , where only two signal sets of different intensities were present. In this case, all ^{13}C - and ^1H -NMR resonances could be assigned to either the minor or major component by an

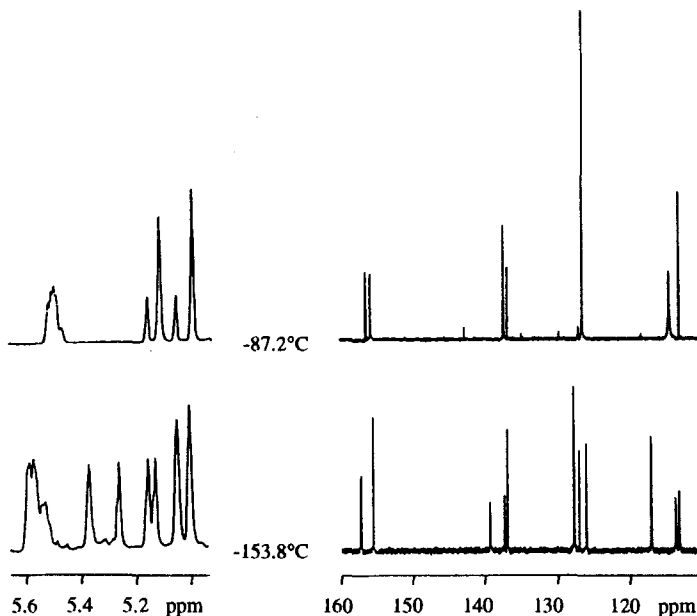


Fig. 1. Partial ^1H - (left) and ^{13}C -NMR spectra (right) of $(-)\text{-}\beta\text{-caryophyllene}$ (1) at -87.2 and -153.8°

analysis of the ^{13}C - and ^1H -NMR spectra in connection with an APT and a HETCOR spectrum. A COSY spectrum confirmed the assignments and revealed the connectivities. The results are summarized in *Table 2*.

Having established the connectivities, we next performed a NOESY experiment at -87.2° and looked for effects allowing an unambiguous assignment of the persisting minor component to one of the four possible conformers. Towards this end, we used the geometries calculated with MM3 [2] and searched for NOEs between vinylic and aliphatic protons caused by H–H distances shorter than 3 \AA [6] and being exclusively significant for one of the four conformers (*Figs. 2 and 3*). Albeit only three NOEs could be detected, the result was clear: A cross peak between H–C(5) and H–C(9) revealed, that the persisting minor component was the $\beta\beta$ conformer ($d = 2.77$ ($\beta\beta$), 3.11 ($\alpha\beta$), 4.10 ($\beta\alpha$), 4.60 \AA ($\alpha\alpha$)). Further effects between H–C(13) and H'–C(10) ($d = 2.21 \text{ \AA}$) and H'–C(13) and H–C(7) ($d = 2.46 \text{ \AA}$) indicated that H–C(13) is aligned with the cyclobutane unit while H'–C(13) points to the opposite direction.

For the major component, the complete set of nine NOEs characteristic for a rapidly equilibrating mixture of the $\alpha\alpha$ and $\beta\alpha$ conformer was observed (*Table 2, Figs. 2 and 3*). Within this set, the cross peaks between H–C(5) and H–C(7) ($d = 2.72$ ($\alpha\alpha$), 3.45 ($\alpha\beta$), 3.98 \AA ($\beta\alpha$)), and H–C(13) and H–C(10) ($d = 2.04$ ($\beta\alpha$), 4.05 ($\alpha\beta$), 4.33 \AA ($\alpha\alpha$)) were exclusively significant for the $\alpha\alpha$ and $\beta\alpha$ conformer, respectively. An intervention of the $\alpha\beta$ conformer could be excluded as no cross peak between H–C(5) and H–C(2) ($d = 2.26 \text{ \AA}$) was observed. It was thus clear that $(-)\text{-}\beta\text{-caryophyllene}$ (1) exists at -87.2° as a mixture of a rapidly interconverting pair of $\alpha\alpha$ and $\beta\alpha$ conformers, and a pure $\beta\beta$ conformer.

Table 2. ^{13}C - and ^1H -NMR Data (δ [ppm]) of (-)- β -Caryophyllene (1) at -87° . Including COSY and NOESY Data. The ranges of the ^1H resonances were determined from the COSY spectrum. Of two protons attached to the same C-atom, the one at higher field is marked as H' .

Atom ^{a)}	$\alpha/\beta\alpha$		$\beta\beta$		NOE	COSY	NOE	^{13}C	^1H	COSY	NOE
	^{13}C	^1H	COSY	NOE							
H-C(1)	54.2	1.88-1.96 (m, 1 H)	H-C(2), H'-C(2)	H-C(5)	H-C(5)	H-C(2)	H-C(5)	57.4	1.64-1.72 (m, 1 H)	H-C(2)	H-C(5)
H-C(2)	31.1	1.61-1.75 (m, 2 H)	H-C(1), H-C(3), H'-C(3)			H-C(1), H-C(3)		33.4	1.86-1.92 (m, 1 H) 1.72-1.77 (m, 1 H)	H-C(1), H-C(3)	
H'-C(2)											
H-C(3)	41.6	2.22-2.30 (m, 1 H)	H-C(2), H'-C(2), H'-C(3)			H-C(2), H'-C(2), H'-C(3)		36.3	2.64-2.70 (m, 1 H) 1.71-1.77 (m, 1 H)	H-C(2), H'-C(2), H'-C(3)	H'-C(3)
H'-C(3)											
C(4)	137.3	2.01-2.14 (m, 1 H)	H-C(2), H'-C(2), H'-C(3)	H-C(5)		H-C(3)		136.8		H-C(3)	
H-C(5)	126.3	5.49-5.54 (m, 1 H)	H-C(6), H'-C(6), H-C(7), H-C(12)	H-C(1), H'-C(3), H'-C(6), H-C(7)		H-C(6)		126.3	5.47-5.49 (m, 1 H)	H-C(6)	H-C(9)
H-C(6)	30.9	2.50-2.58 (m, 1 H)	H-C(5), H'-C(6), H-C(7)	H'-C(13)		H-C(6)		31.6	2.60-2.68 (m, 1 H)	H-C(5), H'-C(6), H-C(7), H-C(12)	
H'-C(6)											
H'-C(6)											
H'-C(7)	36.1	2.32-2.38 (m, 1 H)	H-C(6), H'-C(7)			H-C(6), H'-C(7)		42.2	2.53-2.62 (m, 1 H)	H-C(6), H'-C(7)	
H'-C(7)											
C(8)	156.1	2.10-2.14 (m, 1 H)	H'-C(6), H-C(7)			H-C(7)		156.7	2.04-2.12 (m, 1 H)	H-C(7)	
H-C(9)	50.8	2.56-2.61 (m, 1 H)	H-C(10), H'-C(10)			H-C(10)		51.2	2.42-2.51 (m, 1 H)	H-C(10), H'-C(10)	H-C(5)
H-C(10)	41.6	1.76-1.82 (m, 2 H)	H-C(9)			H-C(9)		44.3	1.90-1.97 (m, 1 H)	H-C(9), H'-C(10)	
H'-C(10)											
C(11)	31.7							34.6	1.72-1.80 (m, 1 H)	H-C(9), H-C(10)	H-C(13)
Me(12)	18.2	1.78 (s, 3 H)	H-C(5)			H-C(5)		24.1	1.75 (s, 3 H)	H-C(6)	
H-C(13)	114.1	5.12 (s, 1 H)	H'-C(13)	H-C(9), H-C(10)		H-C(13)		112.8	5.16 (s, 1 H)	H'-C(13)	H'-C(10)
H'-C(13)											
Me(14)	24.2	1.19 (s, 3 H)						23.6	1.16 (s, 1 H)		
Me(15)	31.6	1.18 (s, 3 H)						31.4	1.17 (s, 3 H)		

^{a)} For numbering, see Fig. 2.

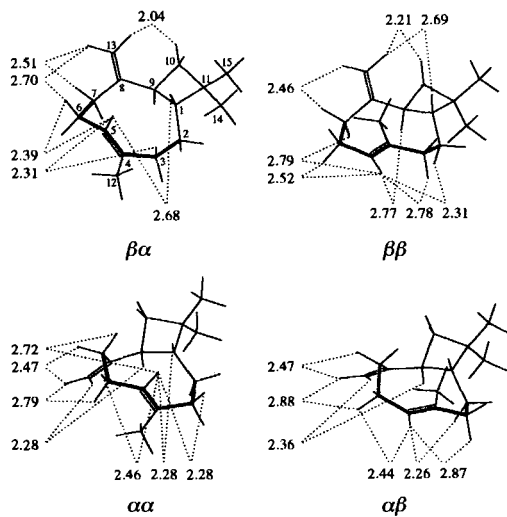


Fig. 2. Geometries of the different conformers of $(-)\beta$ -caryophyllene (**1**) as calculated with MM3 [2]. For each conformer, all distances between vinylic and aliphatic protons shorter than 3 Å are given.

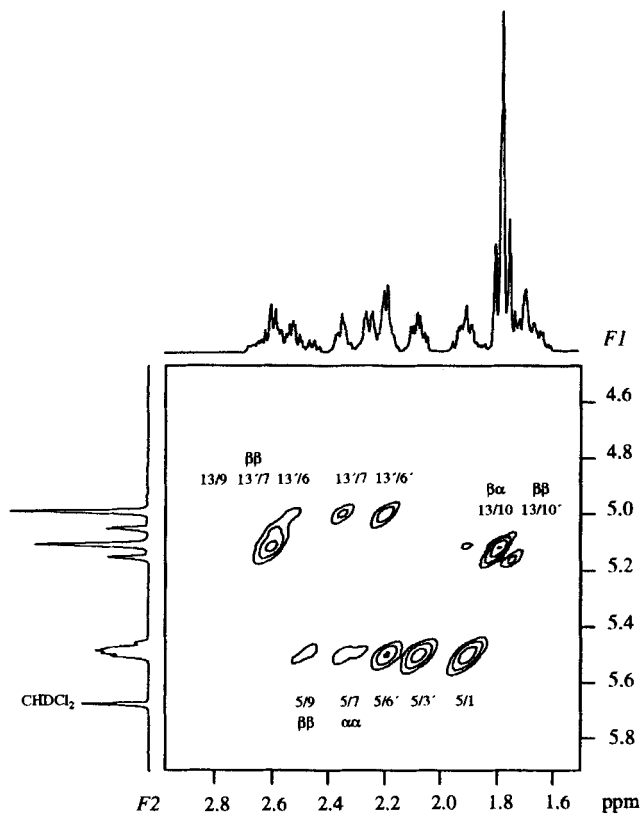


Fig. 3. Partial NOESY spectrum of $(-)\beta$ -caryophyllene (**1**) at -87.2°

2.3. *Identification of the $\alpha\alpha$ and $\beta\alpha$ Conformer.* To complete the conformational analysis of **1**, at least one of the rapidly interconverting conformers $\alpha\alpha$ and $\beta\alpha$ had to be identified. Analogously with the identification of the $\beta\beta$ conformer at -87.2° , this was done by an analysis of the ^{13}C - and ^1H -NMR spectra at -153.8° in connection with an APT, a HETCOR, and a COSY spectrum, and subsequent NOESY experiments. Based on the results of the analysis at -87.2° , all ^{13}C - and ^1H -NMR resonances of the $\beta\beta$ conformer could be identified and the remaining two sets of signals assigned to either the major or minor component of the remaining two conformers. Then the connectivity of the three signal sets was established. The results are given in *Table 3*.

At -153.8° , three instead of two conformers are present and, therefore, only NOEs caused by very short H–H distances could be observed (*Fig. 4*). Of these, a cross peak between H–C(13) and H–C(9) of the most abundant component was exclusively significant for the $\alpha\alpha$ conformer ($d = 2.28 \text{ \AA}$), while the cross peaks between H–C(13) and H'–C(10) ($d = 2.21 \text{ \AA}$) and H'–C(13) and H–C(7) ($d = 2.46 \text{ \AA}$) of the $\beta\beta$ conformer had already been observed at -87.2° . Therefore, the distribution of the different conformers at -153.8° was clear: The highest populated conformer was the $\alpha\alpha$ conformer (48%), followed by the $\beta\alpha$ (28%) and the $\beta\beta$ conformer (24%).

Of the remaining interactions, the cross peaks between H'–C(13) and H–C(6) ($d = 2.79 \text{ \AA}$), and H'–C(13) and H–C(7) ($d = 2.47 \text{ \AA}$) belong to the $\alpha\alpha$ conformer, while the cross peaks between H–C(13) of the $\alpha\alpha$ conformer and H–C(9) of the $\beta\alpha$ conformer, between H–C(13) of the $\beta\alpha$ conformer and H–C(9) of the $\alpha\alpha$ conformer, and between

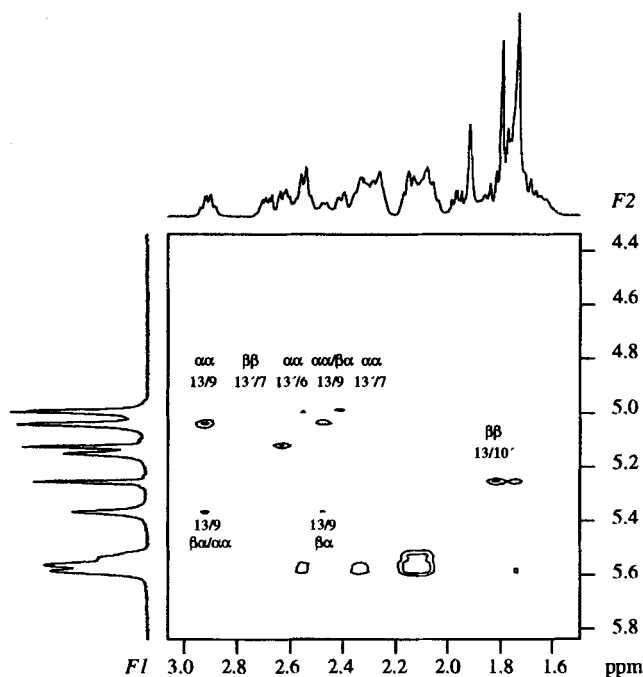


Fig. 4. Partial NOESY spectrum of $(-)\text{-}\beta\text{-caryophyllene (1)}$ at -153.8°

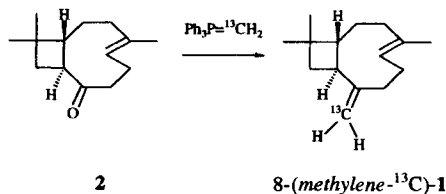
Table 3. ^{13}C - and ^1H -NMR Data of (-)- β -Caryophyllene (1) at -153.8° . Including COSY and NOESY Data. The ranges of the ^1H resonances were determined from the COSY spectrum. Of two protons attached to the same C-atom, the one at higher field is marked as H.

Atom ^{a)}	<i>ax</i>				<i>bx</i>				<i>ax</i>				<i>bx</i>			
	^{13}C	^1H	COSY	NOE	^{13}C	^1H	COSY	NOE	^{13}C	^1H	COSY	NOE	^{13}C	^1H	COSY	NOE
H-C(1)	49.6	2.12-2.18 (m, 1 H)	H'-C(2), H-C(9)		59.6	1.72 (m, 1 H)			57.8	1.72 (m, 1 H)			57.8	1.72 (m, 1 H)		
H-C(2)	30.5	1.74-1.83 (m, 1 H)	H'-C(2), H'-C(3)		30.5	1.80 (m, 2 H)			33.8				33.8			
H'-C(2)		1.58-1.68 (m, 1 H)	H-C(1)							1.86 (m, 1 H)				1.86 (m, 1 H)		
H-C(3)	41.3	2.22-2.30 (m, 1 H)	H'-C(3)		42.7	2.28-2.36 (m, 1 H)	H'-C(3)		36.6	2.66-2.74 (m, 1 H)	H'-C(3)		36.6	2.66-2.74 (m, 1 H)	H'-C(3)	
H'-C(3)		2.02-2.12 (m, 1 H)	H-C(2), H-C(3)			2.08-2.18 (m, 1 H)	H-C(3)		137.3	1.74-1.82 (m, 1 H)	H-C(3)		137.3	1.74-1.82 (m, 1 H)	H-C(3)	
H-C(4)	136.9				139.4				127.0	5.50-5.56 (m, 1 H)	H-C(6), H'-C(6), H-C(12)		127.0	5.50-5.56 (m, 1 H)	H-C(6), H'-C(6), H-C(12)	
H-C(5)	127.8	5.54-5.62 (m, 1 H)	H-C(6), H'-C(6), H-C(12)		126.0	5.52-5.58 (m, 1 H)	H-C(6), H'-C(6), H-C(12)		32.3	2.60-2.66 (m, 1 H)	H-C(5), H'-C(6), H-C(7)		32.3	2.60-2.66 (m, 1 H)	H-C(5), H'-C(6), H-C(7)	
H-C(6)	33.4	2.50-2.60 (m, 1 H)	H-C(5), H'-C(6)		29.1	2.52-2.58 (m, 1 H)	H-C(5), H-C(6)		42.5	2.66-2.72 (m, 1 H)	H-C(6), H'-C(7)		42.5	2.66-2.72 (m, 1 H)	H-C(6), H'-C(7)	H'-C(13)
H'-C(6)		2.30-2.40 (m, 1 H)	H-C(5), H-C(6)			2.04-2.12 (m, 1 H)	H-C(5), H-C(6)		157.4	2.12-2.20 (m, 1 H)	H-C(7)		157.4	2.06-2.12 (m, 1 H)	H-C(5), H-C(6)	
H-C(7)	33.7	2.36-2.46 (m, 1 H)	H'-C(7)		39.6	2.60-2.68 (m, 1 H)	H'-C(7)		49.4	2.40-2.54 (m, 1 H)	2 H-C(10)		51.5	2.50-2.58 (m, 1 H)	2 H-C(10)	
H'-C(7)		2.26-2.34 (m, 1 H)	H-C(7)			2.12-2.20 (m, 1 H)	H-C(7)			2.12-2.20 (m, 1 H)	H-C(7)			2.06-2.12 (m, 1 H)	H-C(5), H-C(6)	
H-C(8)	155.6				157.4				41.5	2.02-2.10 (m, 1 H)	H-C(9), H'-C(10)		44.7	1.92-2.02 (m, 1 H)	H-C(9), H'-C(10)	
H-C(9)	53.1	2.88-2.98 (m, 1 H)	H-C(1), 2 H-C(10)		49.4	2.40-2.54 (m, 1 H)	2 H-C(10)		112.9	5.36 (s, 1 H)	H-C(9)		113.4	5.25 (s, 1 H)	H-C(10)	
H-C(10)	41.8	1.66-1.78 (m, 2 H)	H-C(9)		41.5	2.02-2.10 (m, 1 H)	H-C(9), H'-C(10)		17.6	1.92 (s, 3 H)			24.6	1.80 (s, 3 H)		
H'-C(10)					34.6	1.80-1.92 (m, 1 H)	H-C(9), H-C(10)			5.15 (s, 1 H)				5.12 (s, 1 H)		
H-C(11)	32.5								112.9	5.36 (s, 1 H)	H-C(9)		113.4	5.25 (s, 1 H)	H-C(10)	
H-C(12)	19.4	1.74 (s, 3 H)			17.6	1.92 (s, 3 H)			112.9	5.36 (s, 1 H)	H-C(9)		113.4	5.25 (s, 1 H)	H-C(10)	
H-C(13)	116.9	5.04 (s, 1 H)	H'-C(7)		112.9	5.36 (s, 1 H)	H-C(9)		112.9	5.36 (s, 1 H)	H-C(9)		113.4	5.25 (s, 1 H)	H-C(10)	
H'-C(13)		4.99 (s, 1 H)								5.15 (s, 1 H)	H-C(6), H-C(7)			5.12 (s, 1 H)	H-C(7)	
H-C(14)	23.8	1.26 (s, 3 H)			25.2	1.20 (s, 3 H)			25.2	1.20 (s, 3 H)			24.0	1.21 (s, 3 H)		
H-C(15)	31.8	1.22 (s, 3 H)			31.6	1.23 (s, 3 H)			31.6	1.23 (s, 3 H)			31.9	1.22 (s, 3 H)		

^{a)} For numbering, see Fig. 2.

H–C(13) and H–C(9) of the $\beta\alpha$ conformer indicate, that even at -153.8° the interconversion between the $\alpha\alpha$ and $\beta\alpha$ conformer is fast enough to allow an effective NOE transfer from one conformation to the other.

2.4. *Determination of the Barrier of Inversion between the $\alpha\alpha$ and $\beta\alpha$ Conformer.* For the determination of the barrier of inversion between the $\alpha\alpha$ and $\beta\alpha$ conformer via a bandshape analysis of exchange-broadened ^{13}C -NMR spectra, we prepared 8-(methylene- ^{13}C)-**1**. We obtained this material by high-temperature methylenation [7] of the norcaryophyllene ketone **2** [8] (*Scheme*).



For the bandshape analysis, we recorded a series of seven ^{13}C -NMR spectra between -66.5 and -153.8° (*Fig. 5*). The static parameters (chemical shifts (Hz), populations (%), relaxation times (s): 14616, 51, 0.16 ($\alpha\alpha$); 14188, 22, 0.15 ($\beta\beta$); 14104, 27, 0.15 ($\beta\alpha$)) were taken from the spectrum at -153.8° , and the bandshapes and corresponding rate constants calculated with the program DNMR5 [9] (*Fig. 5*). Insertion of the rate data into the *Eyring* equation and weighted least-square adjustment with the program ACTPAR [10] (*Fig. 6*) yielded the activation parameters for the conversion $\alpha\alpha \rightarrow \beta\alpha$ as $\Delta H^\ddagger = 5.9 \pm 0.3$ kcal/mol, $\Delta S^\ddagger = -8.1 \pm 1.8$ cal/mol \cdot K and $\Delta G_{298}^\ddagger = 8.3 \pm 0.8$ kcal/mol.

3. **Conclusions.** – The conformational behavior of (–)- β -caryophyllene (**1**) was reinvestigated. An analysis of the ^{13}C - and ^1H -NMR spectra at -87.2 and -153.8° in connection with APT, HETCOR, COSY, and NOESY spectra revealed, that **1** adopts the conformations $\alpha\alpha$ (48%), $\beta\alpha$ (28%), and $\beta\beta$ (24%), with $\alpha\alpha$ and $\beta\alpha$ rapidly interconverting down to -100° . The activation parameters for the conversion $\alpha\alpha \rightarrow \beta\alpha$ were determined from a bandshape analysis of exchange-broadened ^{13}C -NMR spectra of 8-(methylene- ^{13}C)-**1** to give $\Delta H^\ddagger = 5.9 \pm 0.3$ kcal/mol, $\Delta S^\ddagger = -8.1 \pm 1.8$ cal/mol \cdot K, and $\Delta G_{298}^\ddagger = 8.3 \pm 0.8$ kcal/mol. Together with the previously determined activation parameters $\Delta H^\ddagger = 14.7 \pm 0.2$ kcal/mol, $\Delta S^\ddagger = -4.5 \pm 0.6$ cal/mol \cdot K, and $\Delta G_{298}^\ddagger = -16.1 \pm 0.3$ kcal/mol for the conversion $\beta\alpha \rightarrow \beta\beta$ [5], which are in fact the parameters for the conversion $\alpha\alpha \rightarrow \beta\beta$, all extrema of the inversion potential curve of (–)- β -caryophyllene (**1**) are now known. Of the different force fields used to describe the conformational behavior of **1** (MM1 [4], MM2 [3] [11], MM3 [2] [12], MMX [5], SYBIL [13]), MM3 performs best. However, in other cases, this may be different.

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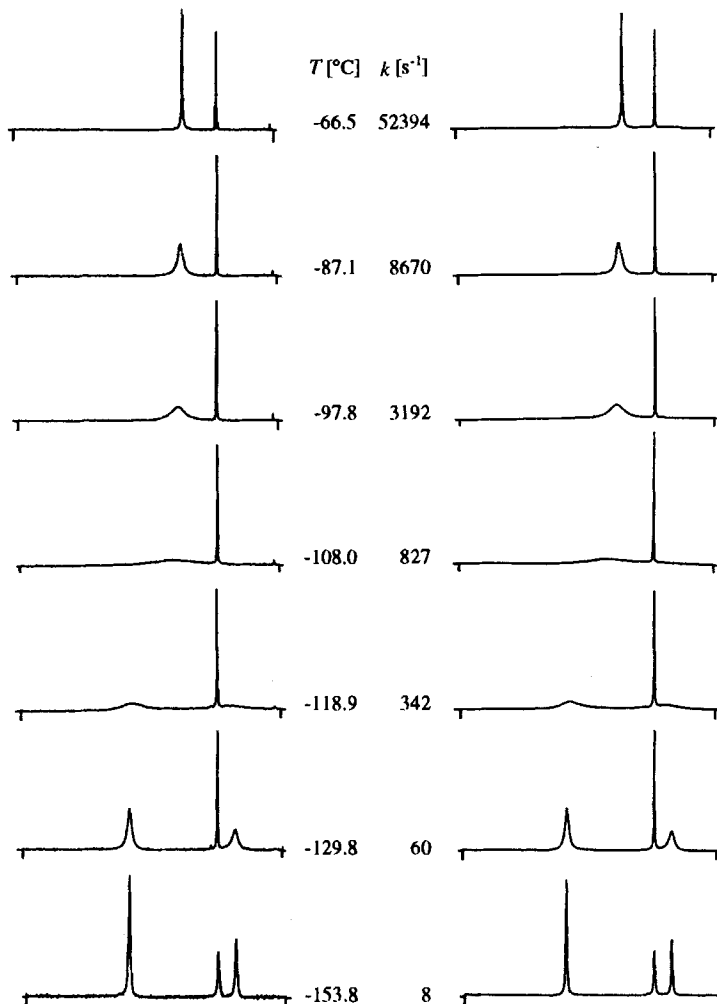


Fig. 5. Experimental (left) and computed bands (right) of the ^{13}C -NMR spectrum of 8-(methylene- ^{13}C)-1 at different temperatures and corresponding rate constants derived therefrom

Experimental Part

General. [^{13}C]Methyl]triphenylphosphonium iodide (99 atom-% ^{13}C ; m.p. 176°) was obtained by treating Ph_3P (18.4 g, 70 mmol) in dry benzene (60 ml) with (^{13}C)methyl iodide (10.0 g, 70 mmol, 99 atom-% ^{13}C) for 72 h at r.t. (yield 98%). (D_6)Dimethyl ether was prepared by slow addition of (D_4)methanol (30 ml) to conc. H_2SO_4 soln. (19.5 ml) under N_2 with stirring, while the temp. was gradually raised from 0 to 150°. The evolving (D_6)dimethyl ether passed a condenser and a drying tube and was trap-to-trap distilled prior to use. Anal. GC: Carlo-Erba-GC-6000-Vega-2 instrument, split/splitless injector, FID 40 detector; H_2 as carrier gas; t_{R} in min. Prep. GC instrument as for anal. GC; thermal conductivity detector; H_2 as carrier gas; product ratios were not corrected for rel. response. TLC: Macherey & Nagel Polygram SIL G/UV254 plates; colorless substances were detected by oxidation with 3.5% alcoholic molybdophosphoric acid and subsequent warming.

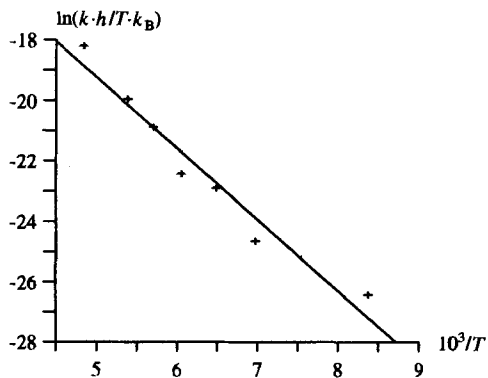


Fig. 6. Weighted least-squares adjustment of the rate data to the Eyring equation

NMR Measurements. All NMR spectra were obtained with a Varian-VXR-500 spectrometer equipped with a variable-temp. probe. The temp. calibration was performed with a temp. sensor consisting of a 1.8 mm diameter high precision Pt 100 resistor at the end of a glass rod which was introduced in a 5 mm o.d. dummy tube containing pent-1-ene such that the active zone (15 mm length) was precisely positioned at the height of the receiver coil. The delay times for the calibrations and the measurements were 30 min between -153.8 and -108.0° and 15 min between -108.0 and -66.5° . The spectra at -153.8° were obtained with solns. of 50 mg (^{13}C , HETCOR), 10 mg (^1H , NOESY), and 4 mg of **1** (COSY), resp. in 500 μl of $(\text{CD}_3)_2\text{O}$. The spectra above -153.8° were obtained with solns. of 25 mg (^{13}C , HETCOR), 5 mg (^1H , COSY), and 4 mg of **1** (NOESY), resp., in 500 μl of $(\text{CD}_3)_2\text{O}/\text{CD}_2\text{CD}_2$ 3:1. The exper. spectra for the bandshape analysis were obtained with a soln. of 3.0 mg of 8-(methylene- ^{13}C)-**1** in 500 μl of $(\text{CD}_3)_2\text{O}$. All samples were degassed and sealed under vacuum. As standards, the following chemical shifts were used: $\delta_{\text{H}}(\text{CD}_3\text{OCD}_2\text{H})$ 3.40 ppm, $\delta_{\text{C}}(\text{CD}_3\text{OCD}_3)$ 60.90 ppm.

(1*R*,9*S*,4*E*)-4,11,11-Trimethyl-8-[(^{13}C)methylene]bicyclo[7.2.0]undec-4-ene (8-(methylene- ^{13}C)-**1**). To a stirred suspension of K(*t*-BuO) (209 mg, 1.86 mmol) in dry benzene (3.75 ml) under N_2 , [(^{13}C)methyl]triphenylphosphonium iodide (810 mg, 2.10 mmol; 99 atom-% ^{13}C) was added and the mixture heated to reflux. After 1 h, most of the benzene was distilled off under N_2 until the temp. of the remaining dark yellow slurry reached 120° . Norcaryophyllene ketone **2** (50 mg, 25 mmol; purity 93%) was added and the temp. maintained until capillary GC (30 m \times 0.32 mm i.d. deactivated fused-silica capillary column coated with 0.25 μm DB FFAP; 10 min 120° , 20 $^\circ$ /min to 140° , 5 min 140° , 0.6 bar of H_2 ; t_{R} 3.14, 3.42 (8-(methylene- ^{13}C)-**1**), 12.56 (**2**), 13.41) indicated that the reaction was complete (4 h). The mixture was diluted with pentane (3.75 ml) and hydrolyzed with H_2O (0.37 ml). The org. layer was decanted, the residue extracted with pentane (3 \times 10 ml), the combined org. layers concentrated (bath temp. 20° , 20 Torr) and the residue (180 mg) chromatographed (silica gel, 15 \times 2 cm, pentane; R_{f} 0.49) to give 42 mg (82%) of crude 8-(methylene- ^{13}C)-**1** (purity 93%) as colorless liquid. Pure 8-(methylene- ^{13}C)-**1** was obtained by prep. GC (3 m \times 1/4 inch all-glass system, 15% SE 30 on Chromosorb W AW/DMCS, 60–80 mesh, 150°): t_{R} 1.00, 1.23 (8-(methylene- ^{13}C)-**1**). ^1H -NMR (25 $^\circ$, 500 MHz, CD_3OCD_3 , ref. $\text{CD}_3\text{OCD}_2\text{H}$): 5.01 (*d*, $^1J(\text{CH}) = 153$, 0.76 H); 5.12 (*d*, $^1J(\text{CH}) = 153$, 0.24 H); 5.15 (*d*, $^1J(\text{CH}) = 153$, 0.24 H); 5.17 (*d*, $^1J(\text{CH}) = 153$, 0.76 H). ^{13}C -NMR (25 $^\circ$, 125 MHz; CD_3OCD_3 , ref. CD_3OCD_3): 114.0, 112.9 (*sec.* C).

Supplementary Material. – Temperature-dependant ^1H -NMR, ^{13}C -NMR, APT, HETCOR, COSY, and NOESY spectra of **1** and minimum structures (MM3 format) and listings of the conformers $\alpha\alpha$, $\beta\alpha$, and $\alpha\beta$ (29 pages) may be obtained from the authors on request.

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