Assignment of Relative Configuration to Acyclic Compounds Based on ^{13}C NMR Shifts. A Density Functional and Molecular Mechanics Study

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1,3-Dimethylated hydrocarbon segments occur frequently as structural elements in polyketide natural products. The ^{13}C NMR chemical shifts of a series of model compounds containing such segments can be well reproduced by a combination of molecular mechanics and SOS-DFPT/IGLO calculations. ^{13}C NMR chemical shifts are calculated on MM3 geometries and are Boltzmann weighted according to the MM3 energies. On the basis of the resulting thermally averaged chemical shifts, all diastereomers of the model compounds can be unequivocally distinguished. Significant differences in chemical shifts occur at methyl groups and methylene groups that are adjacent to a single stereogenic center. The method is applied to predict the relative configuration of two stereocenters in the side chains of two natural products, sambutoxin and the bradykinin inhibitor L-755,897.

Introduction

The calculation of NMR chemical shifts from first principles has become a powerful method to solve structural problems in organic chemistry.[1] ^{13}C NMR chemical shifts depend strongly on molecular geometry, which for flexible chain compounds is governed by the relative configuration of stereocenters and by conformational behavior. If the relative configuration of all stereocenters is known, the comparison of calculated and experimental shifts can lead to statements about conformation. This is done in the field of protein structure refinement,[2] where first steps have been undertaken toward theoretical shielding surfaces[3] of proteins. In contrast, upon isolation of a new natural product containing a flexible carbon chain, it is the primary goal to determine the relative configuration of all its stereocenters. Again, this could be achieved by comparison of calculated and experimental ^{13}C NMR chemical shifts, provided that the conformational behavior of all conceivable diastereomers can be reliably calculated by a theoretical model. We were interested to analyze the relation between relative configuration and ^{13}C NMR chemical shifts in partially unsaturated, 1,3-dimethylated hydrocarbon sequences that occur frequently as segments in polyketide natural products.[4] Up to now, the calculation of *ab initio* ^{13}C NMR data of conformationally flexible hydrocarbon compounds has been restricted to small systems. IGLO[5] and GIAO[6] methods have been applied to n-alkanes,[7] focussing on a discussion of gauche effects and empirical functions to reproduce the conformational dependence of the calculated shieldings. For organic compounds comprising larger carbon skeletons with multiple stereocenters, the interpretation of chemical shifts has mainly been done by means of empirical increment systems.[8] Increments developed by Beierbeck and Saunders[9] and by Whitesell and co-workers[10] have been applied to some 3,5-dimethylated hydrocarbons and alcohols (e.g. **1**, **3**). Parameters were derived from rigid ring systems with known configuration. This necessarily limits the applicability of such approaches to saturated hydrocarbon skeletons and parametrization is tedious. We therefore sought to find a computational procedure which makes use of accurate quantum chemical calculations, yet is efficient enough to help experimentalists in answering questions of current interest. We show here that the use of an SOS-DFPT/IGLO approach together with MM3 geometries and energies meets this goal. Density functional methods for the calculation of shielding constants are an obvious choice, as they are proven to give better results for most organic molecules at reduced computational cost.[11] The method is applied to elucidate the relative configuration in the side chains of two recently isolated natural products, sambutoxin (**12**) and the bradykinin inhibitor L-755,807 (**19**).

Computational Methods

The conformational space of all investigated compounds was explored by the MCMM method[12] using the

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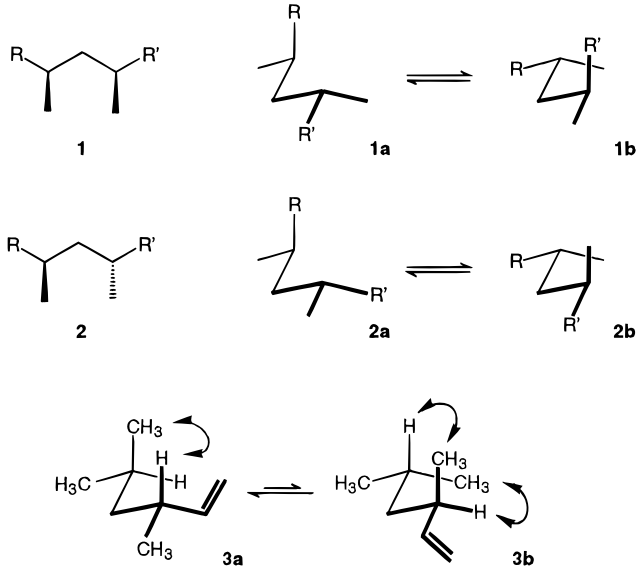
MM3* force field as implemented in MACROMODEL 4.5.[13] All dihedral angles along the carbon chain were subjected to the search, which was run for 1500 to 4000 steps for four to six rotatable bonds, respectively. All local minima were further minimized by the full matrix Newton Raphson minimizer of MM3(94).[14] The ^{13}C NMR shielding constants were calculated for the low-lying minima (from 2 to 20, depending on the case) whose population constituted 78−99% of the total Boltzmann distribution at 298 K according to the MM3 energies. All calculations were carried out with the deMon NMR program, which uses the SOS-DFPT approach[15] in conjunction with the deMon Kohn−Sham program.[16] The Loc.1 approximation,[15] the Perdew-Wang-91 exchange correlation potential,[17] the IGLO-II basis set,[5] and the iglo-3 auxiliary basis set were employed except where mentioned otherwise. The NMR calculations accounted for 2 h of CPU time on an IBM SP2 for a system comprising 9 non-hydrogen atoms and 11 h for model compounds comprising 17 non-hydrogen atoms (8 h and 2 d on a 150 MHz SGI R4400, respectively). The calculated shielding constants were subtracted from the calulated value of TMS (188.6 ppm) to obtain *d* values, which were then weighted according to a Boltzmann distribution at 298 K.

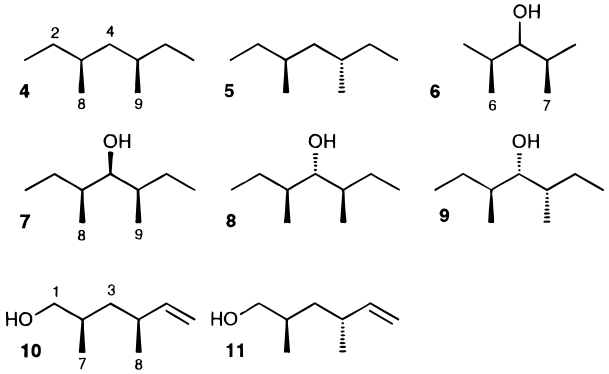
Results and Discussion

Recurring elements in many polypropionate natural products are the 2,4-dimethylated pentane segments **1** and **2**, which may in addition be oxygenated in the 3-position. The structures **1** and **2** are two constitutionally identical stereoisomers. Both **1** and **2** populate only two local conformations a and b because any other diamond lattice conformation will lead to destabilizing syn-pentane interactions (Scheme 1). Except when R = R′ in **1**, the a and b conformers have different energies and will be populated to a different extent. Since in **2a** the groups R and R′ have one additional gauche interaction relative to conformation **2b** and in the latter both methyl groups have one more gauche interaction than in **2a**, the difference in effective size between R and CH_3 will affect the position of the conformer equilibrium. If R′ is smaller than a methyl group, conformer **2a** will be favored. This can be illustrated with reference to compound **3**, for which the equilibrium is calculated to lie on the side of **3a**. Conformation **3a** has the bulky methyl group in the "end-of-chain" position and the slimmer vinyl group in the sterically more encumbered "bent" position. This effect resembles Newman's "rule of six".[18] In fact, a 1.5:1 preference for **3a**:**3b** has been deduced from vicinal $^3J_{HH}$ coupling constants.[19]

Scheme 1. For Syn and Anti 2,4-Dimethylated Pentanes, Only Two Conformations Avoid Syn-Pentane Interactions (1, 2). Double Bonds Preferentially Adopt the Bent Position (3)



Scheme 2. Model Compounds for the Calculation of ^{13}C NMR Chemical Shifts. Results of the NMR Calculations Are Shown in Table 1



Model Compounds. Since the ^{13}C NMR chemical shifts differ for the individual conformers, a prediction of experimental chemical shifts for such open chain compounds requires a knowledge of the chemical shifts for the individual conformers and of the conformer equilibrium. We chose a set of model compounds **4**−**11** (Scheme 2) to compare calculated ^{13}C NMR chemical shift with those measured experimentally. The conformer equilibria were calculated based on MM3 energies. In the case of the alkenes **10** and **11** we consider the MM3 energies to be reliable since Houk has shown for 3-methyl-1-butene and for 4-methyl-2-pentene that rotational barriers of MM3 are in good agreement with ab initio data.[20] As a further test, we performed ab initio geometry optimizations of the **10** lowest lying minima of **10** and **11**. On the MP2//HF/TZ+2P level we found excellent agreement between the MM3 and ab initio calculated relative energies. Furthermore, the relative energies of all conformers should not change significantly when being transferred from the gas phase into $CDCl_3$ solution, because intramolecular interactions other than van der Waals interactions are absent.

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Table 1. Experimental and Calculated (SOS-DFPT/IGLO) ^{13}C NMR Shifts of Compounds 4−11[a]

		low energy conformers, *n* (%)	δ carbon atom								
			1	2	3	4	5	6	7	8	9
4	exp[b]		11.1	29.5	32.0	44.5	32.0	29.5	11.1	19.6	19.6
	calcd	8 (78)	17.1	36.7	39.8	50.9	39.8	36.7	17.1	24.5	24.5
5	exp[b]		10.9	30.5	31.9	44.3	31.9	30.5	10.9	18.9	18.9
	calcd	9 (81)	17.5	38.3	40.2	50.6	40.2	38.3	17.6	23.9	23.9
6	exp[c]		19.7	30.5	81.7	30.5	19.7	16.8	16.8	–	–
	calcd	2 (96)	25.2	38.8	88.1	38.8	25.2	22.3	22.3	–	–
7	exp[d]		11.5	26.3	36.9	77.8	36.9	26.3	11.5	13.8	13.8
	calcd	8 (92)	17.0	34.2	44.5	84.7	44.5	34.2	17.0	19.3	19.3
8	exp[d]		11.6	23.4	37.1	80.3	37.1	23.4	11.6	16.0	16.0
	calcd	10 (92)	17.7	31.6	44.5	89.0	44.5	31.6	17.7	21.3	21.3
9	exp[d]		11.8	24.9	37.6	78.2	36.6	27.1	11.2	15.3	12.3
	calcd	9 (92)	17.5	32.9	44.9	86.0	44.9	34.7	17.5	20.9	18.2
10	exp[e]		68.4	33.3	40.2	35.4	–	–	21.3	16.2	–
	calcd	11 (86)	77.9	40.6	47.7	45.8	–	–	27.1	21.2	–
11	exp[e]		68.1	33.2	40.2	35.1	–	–	20.0	16.9	–
	calcd	11 (84)	75.1	40.0	47.8	45.8	–	–	26.5	22.9	–

[a] Shifts were calculated for the given number *n* of low energy conformers and Boltzmann weighted at 298 K. Numbers in parentheses give the percentage of the total population that is covered by the *n* conformers. [b] Reference 9a. [c] This work. [d] Reference 10a. [e] Reference 18.

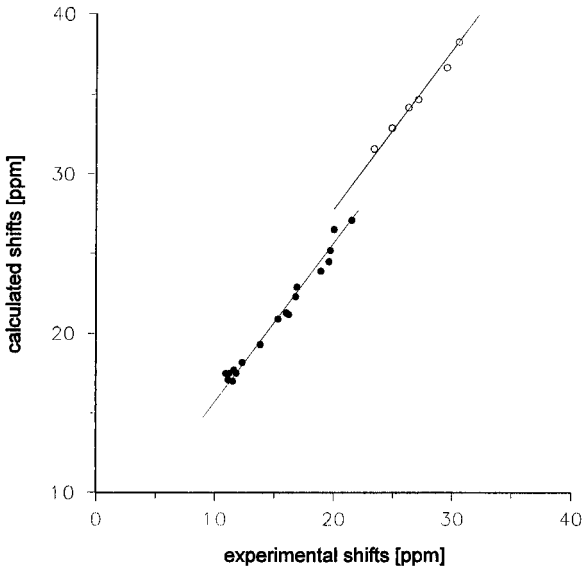

Figure 1. Plot of calculated vs experimental ^{13}C NMR shifts for methyl groups (filled circles) and methylene groups (open circles) that are adjacent to one stereogenic center. Data are for compounds **4**−**11** (Table 1). Methylene and methyl groups show an average offset of 7.8 and 5.7 ppm, respectively.

The results obtained are compiled in Table 1 and compared with the experimental ^{13}C NMR chemical shifts. Linear regression of the data in Table 1 yields a correlation coefficient of 0.996 between theoretical and experimental values. This is a very high correlation considering the fact that the experimental data have not been measured under identical conditions. A closer look at Table 1 reveals, however, that only methyl groups and methylene groups adjacent to a single stereocenter show diagnostic differences between the diastereomers. Figure 1 shows a plot of calculated vs experimental ^{13}C NMR chemical shifts for methyl groups (filled circles) and methylene groups (open circles). There is an offset of several ppm in the calculated values which is lower for the methyl groups (5.7 ppm average) than for the methylene groups (7.8 ppm average). In order to test a possible basis set dependence of these results, we calculated the chemical shifts for model compounds **4**, **5** and **7**−**9** with the larger IGLO III basis set[5] and applied the same averaging procedure as described above. Comparison with the experimental data gave an equally good correlation as with the IGLO II basis, the offset for methyl groups being 3.9 ppm and for methylene groups 7.0 ppm. The systematic difference between calculated and experimental ^{13}C NMR chemical shifts is therefore no basis set effect but must be attributed to the MM3 geometries. Regardless of the origin of this systematic difference, Figure 1 can be used as a calibration curve. In all subsequent discussions we have therefore subtracted 5.7 ppm from the chemical shifts calculated for methyl groups and 7.8 ppm from the chemical shift calculated for methylene groups in order to facilitate the comparison between calculated and experimental data.

It is important to note that the agreement between calculated and experimental ^{13}C chemical shifts is good enough to reproduce the differences between stereoisomers such as **4** and **5**, between **7**, **8**, and **9**, or between **10** and **11**. The most striking experimental distinction between **10** and **11** is the shift difference between the methyl signals. It is larger for the syn compound, a fact well reproduced by the calculations.

The good agreement between calculated and experimental shifts, especially those which are diagnostic for the individual stereoisomers, encouraged us to see whether our calculations would allow predictions as to the relative configuration of type **1** and **2** subunits in natural products. One case of interest is the mycotoxin sambutoxin (**12**) which has recently been isolated from *Fusarium sambucinum*.[21] Its structure has been thoroughly investigated by NMR spectroscopy. NOE experiments established the relative configuration of the stereocenters in the central pyran ring: all three substituents are equatorial, forcing a rigid chair conformation upon the pyran ring. For this reason the aryl-pyridone moiety cannot encounter close contact with the heptenyl chain and the conformational properties of the heptenyl side chain should not depend on the pyridone moiety. The point of interest is that it had not been possible to determine the relative configuration of the two stereocenters in the heptenyl chain by the standard NMR techniques used.

Relative Configuration C-14/C-16 in Sambutoxin (12). For the model compounds **13**−**18** we use the same atom numbering as for sambutoxin. We performed calculations for the model compounds **13** and **14** to see

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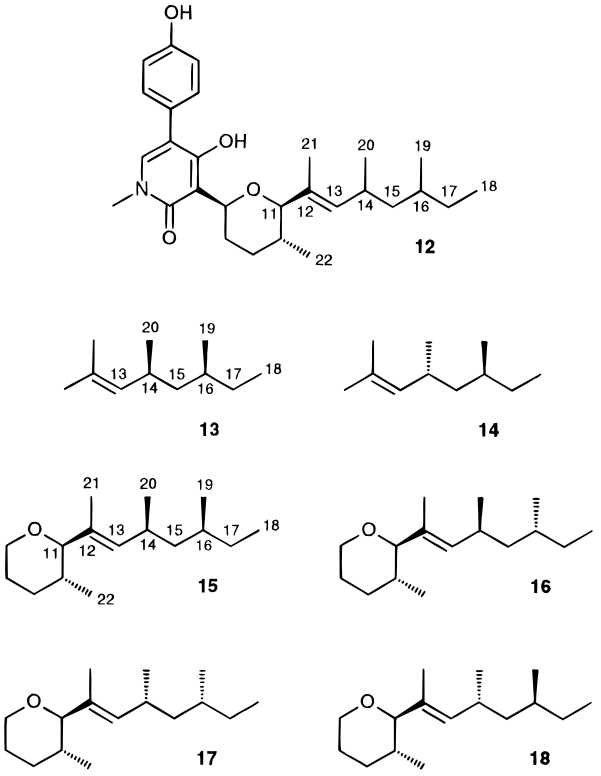
Scheme 3. Sambutoxin (12) and Model Compounds with Different Relative Configurations[a]



[a] The atom numbering of 12 is also used for the Model Compounds. Calculated ^{13}C NMR chemical shifts are given in Table 2.

whether a C-14/C-16 syn arrangement in sambutoxin could be distinguished from a C-14/C-16 anti arrangement. The calculated chemical shifts for **13** and **14** show significant differences only for C-17, C-19, and C-20. In the anti arrangement (**14**), the difference between the two methyl signals is 1.5 ppm, similar to the one found in sambutoxin (1.1 ppm), whereas for the syn isomer **13** the difference is 3.2 ppm. This parallels the situation calculated and found in the reference compounds **10** and **11**. The origin of the different methyl and methylene shifts in **13** and **14** can be traced to the various conformers by looking at five low energy conformers for each system. These are shown in Scheme 4 together with the corresponding calculated chemical shifts (corrected values).

In both compounds, the position of the double bond relative to the carbon chain is fixed due to 1,3-allylic strain.[22] For **13** there are three conformations **13a**−**c** which correspond to **1a**. The three conformations differ only by rotations of the ethyl end group. **13d** and **13e** correspond to the backbone conformation **1b**. There are only two low energy rotamers in the ethyl group possible, since the third would lead to a syn-pentane interaction. One should note the low field shift of C-19 in **13a** and **13c**, which can be qualitatively understood following the argument of Whitesell.[10] When going to **14** the same local conformations that lead to the low field shift of C-19 in **13a** and **13c** are found at higher energy (**14d**, **14e**) and are therefore of less importance for the average shift of **14**. The opposite trend is observed for C-20. In an end-of-chain position, the signal of this methyl group is

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Table 2. Selected Experimental ^{13}C NMR Shifts of the Side Chain of Sambutoxin (12) and Calculated (SOS/DFPT-IGLO) Shifts of the Corresponding Carbon Atoms in the Model Compounds 15−18[a]

	12[b]	**15**	**16**	**17**	**18**
n (%)	−	9 (80)	12 (82)	7 (82)	8 (81)
δ C17	28.9	31.3	28.3	31.5	27.7
δ C19	19.5	18.4	19.4	18.1	19.8
δ C20	20.6	21.3	20.9	21.0	20.5
δ C21	11.6	13.1	12.8	11.4	11.6

[a] Shifts were calculated for the number *n* of MM3 conformers and Boltzmann averaged, covering the percentage of the conformer population given in parentheses. An increment of 7.8 ppm for methylene groups and 5.7 ppm for methyl groups has been subtracted from the calculated values. [b] Reference 21.

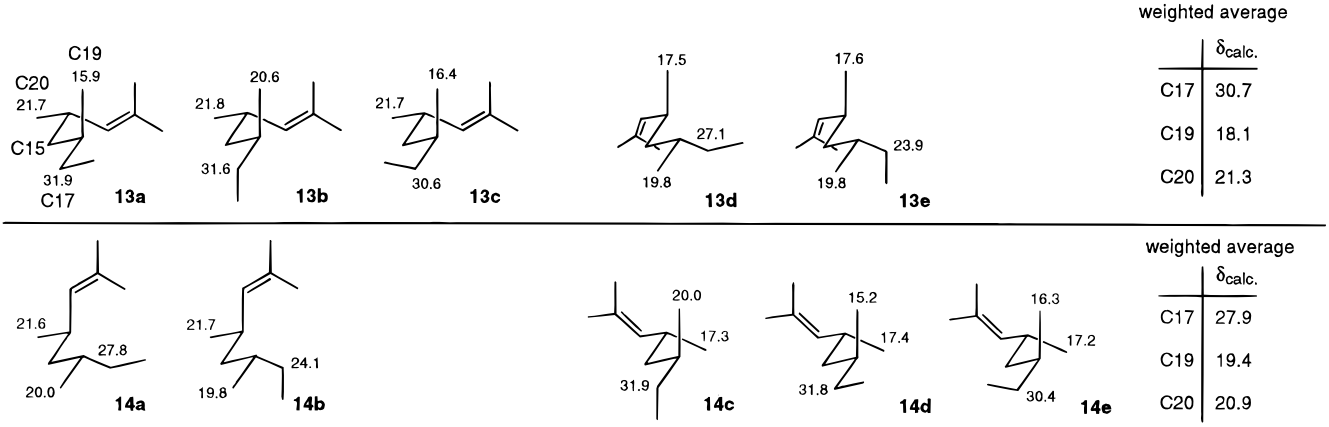
by more than 4 ppm further downfield than in the bent position. Because there is a 3:2 relationship between the ethyl group rotamers of **13** and **14** that have C-20 in the end-of-chain position, this results in a lower average shift for C-20 in **14**. Taking into account the different populations of the individual conformers this leads to a large difference between the chemical shifts of C-20 and C-19 in **13** and to a small gap in **14**. A similar argument can account for the chemical shift of C-17. The calculations on the model compounds **13** and **14** suggest that predictions could be made for the relative configuration of the side chain of sambutoxin from the chemical shifts of C-17, C-19, and C-20.

To approach this problem we calculated conformer populations for the sambutoxin model compounds **15**−**18**. The tetrahydropyran ring was kept fixed in one chair conformation with both substituents in equatorial position, and only the permutation of the five dihedral angles in the side chain between C-11 and C-17 was allowed. Using the computational procedure described above and a cutoff of 30 kJ/mol in the MCMM calculation a total number of ca. 140−150 conformations for each of the stereoisomers **15**−**18** were found. More than 80% of the conformer population was represented by the nine lowest energy conformers in the case of **15**, twelve in the case of **16**, seven in the case of **17**, and eight in the case of **18**.

The conformational behavior of all four compounds can be understood by dividing them into three segments with conformational preferences: The heptenyl chain underlies the "rule of six" restrictions that have been described above in detail for compounds **13** and **14**. The four to five lowest energy conformations have the double bond in the bent position, cf. **13a**−**c**. These conformations account for around 60% (**16**, **18**) and 75% (**15**, **17**) of the total conformer distribution. The dihedral angle at the C13−C14 bond is subject to control by 1,3 -allylic strain as in compounds **13** and **14**. Finally, there exist two rotamers of the heptenyl chain relative to the pyran ring. One of these is strongly disfavored, because it suffers from 1,2-allylic strain between the C-11 hydrogen and the C-21 methyl group (Scheme 5). Thus, apart from the freely rotating ethyl group (C-17,C-18), the four model compounds show significant conformational preferences.

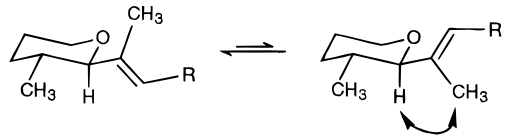
The calculated ^{13}C NMR chemical shifts of **15**−**18** are shown in Table 2 (corrected values). From the comparison with the experimental shifts of sambutoxin (**12**) it follows clearly that sambutoxin cannot contain a 14,16-syn-dimethyl arrangement. In particular, the small experimental shift difference between the two methyl groups C-19 and C-20 (1.1 ppm) corresponds to that calculated for the methyl groups in 16 (1.5 ppm) or 18 (0.7 ppm). In contrast, for the compounds **15** and **17**, this

Scheme 4. Low-Energy Conformations of Model Compounds 13 and 14, Numbered According to Their Energetic Order (MM3). On the Left, Conformations with the Double Bond in the Bent Position Are Depicted[a]



[a] An increment of 5.7 and 7.8 ppm has been subtracted from the calculated ^{13}C NMR chemical shifts of methyl groups and methylene groups, respectively.

Scheme 5. 1,2-Allylic Strain in the Sambutoxin Model Compounds 15−18



difference is calculated to be much larger (2.9 ppm). Further differentiation between the two anti structures **16** and **18** could be possible on the basis of the C-17 and C-21 shifts. In **15** and **16**, where C-11 and C-14 have *Ul* configuration, C-21 shifts are significantly further downfield (≈1.5 ppm) than in **17** and **18**, and they deviate more strongly from the experimental value of sambutoxin. However, the C-21 shift may vary somewhat between the model compounds and sambutoxin itself due to the substitution of the pyran ring. The C-17 shift, on the other hand, is close to the experimental value only for model compound **16**. Compound **16** therefore seems to be the most likely candidate to represent the relative configuration of sambutoxin.

Relative Configuration of C-18/C-20 in L-755,807 (19). Compound **19** has recently been isolated from *Microspaeropsis* sp. and has been reported to be a bradykinin inhibitor.[23] It consists of a γ-lactam ring connected by three conjugated trans double bonds to a heptenyl chain of the same constitution as in sambutoxin.

Compounds **20** and **21** seemed to be suitable models for the elucidation of relative configuration within this subunit. Both compounds are conformationally more mobile than the sambutoxin models **15**−**17** (249 conformers for **20**, 239 conformers for **21** using a cutoff of 30 kJ/mol in the conformational analyses). This is due to the s-cis/s-trans isomerism at the C-15−C-16 bond and to additional "wagging" of the butadienyl chain with attending small rotations of the C-25 methyl group. The results of the deMon calculations are presented in Table 3. Two of the three diagnostic ^{13}C NMR chemical shifts (C-21, C-23) in **20** are very close to the observed shifts of **19**. The agreement is less satisfactory for the C-24 methyl group. However, it can still be clearly concluded that the C-18/C-20 stereocenters in compound **19** have

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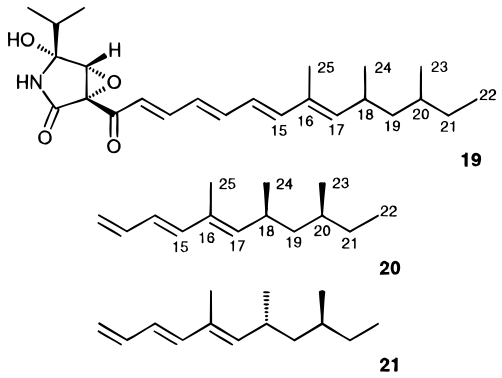
Scheme 6. Structure of the Bradykinin Inhibitor L-755,897 (19) and of the Model Compounds 20 and 21[a]



[a] The atom numbering of 19 is also used for the model compounds. Calculated ^{13}C NMR Shifts Are in Table 3.

Table 3. Selected Experimental ^{13}C NMR Shifts of the Side Chain of the Bradykinin Inhibitor 8 and Calculated (SOS/DFPT-IGLO) Shifts of the Corresponding Carbon Atoms in the Model Compounds 9[a]

	19[b]	20	21
n (%)	–	20 (91)	20 (88)
δ C21	30.4	30.9	29.3
δ C23	19.2	19.2	19.6
δ C24	21.4	20.4	19.7

[a] Shifts were calculated for the number n of MM3 conformers given in the first line and Boltzmann averaged, covering the percentage of the conformer distribution given in parentheses. An increment of 7.8 ppm for methylene groups and 5.7 ppm for methyl groups has been subtracted from the calculated values. [b] Reference 23.

the relative syn configuration. The shift difference between the two methyl groups at the stereogenic centers (C-23, C-24) is again calculated to be greater for the syn model 20 than for the anti model **21**. However, it should be noted that in spite of the similarity of the side chains in **12** and **19**, a simple comparison of their experimental chemical shifts would have led to no conclusion concerning the relative configurations, because the energetic order as well as the chemical shifts of the single conformers depend strongly on small variations in the molecule.

Summary and Conclusions

A combination of molecular mechanics (MM3) and density functional (SOS-DFPT/IGLO) methods, followed by Boltzmann averaging of the calculated chemical shifts, yields reliable ^{13}C NMR chemical shifts for 1,3-dimethylated hydrocarbon chains. All diastereomers of the model compounds **4**−**11** could be clearly distinguished. This allows the prediction of relative configuration to natural products containing such segments. Calculations on the side chains of compounds **12** and **19** show clearly that **12** contains an anti-configured heptenyl chain, whereas the corresponding stereocenters in **19** are of relative syn configuration.

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