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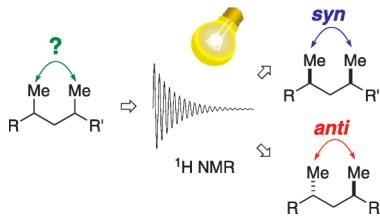
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Assignment of Relative Configuration of Desoxypropionates by ^1H NMR Spectroscopy: Method Development, Proof of Principle by Asymmetric Total Synthesis of Xylarinic Acid A and Applications

2012–18/23



Unraveling the unknown: Interpretation of methylene-proton NMR signals of 1,3-dimethyl-substituted alkyl chains allows for the assignment of the relative configuration of the two adjacent stereogenic centers (see figure). The new method is applicable in various NMR solvents and general trends and rules for assignment are shown. Natural products with unknown configuration can be assigned by using the information gained from already published spectra.



Assignment of Relative Configuration of Desoxypropionates by ^1H NMR Spectroscopy: Method Development, Proof of Principle by Asymmetric Total Synthesis of Xylarinic Acid A and Applications

Yvonne Schmidt, Konrad Lehr, Lucie Colas, and Bernhard Breit*^[a]

Abstract: The determination of the relative configuration of 1,3-dimethyl-substituted alkyl chains is possible by interpretation of ^1H NMR shift differences. Additionally, assignments are feasible in a variety of deuterated solvents, because the corresponding shift differences are not significantly influenced by the solvent. The trends for $\Delta\delta$ values depending on functional groups adjacent to the stereogenic centers are shown. Based on a thorough compari-

son with literature data, the relative configuration of natural products can be predicted. For this purpose, we derived an empirical rule for the ranges in which $\Delta\delta$ values usually occur. Furthermore, we were able to proof the validity of our method by the success-

Keywords: natural products • NMR analysis • polyketides • relative configuration • structure elucidation

ful prediction of the relative configuration for the polyketide natural product xylarinic acid A, which was confirmed by the asymmetric total synthesis of its enantiomer. Based on the proposed simple analysis of published ^1H NMR data and the determination of the relevant chemical-shift differences, we predicted the relative configurations of several previously unassigned natural products.

Introduction

To date, complex natural products, as they are produced by higher plants, microbes, and other organisms, are an abundant source for new leads in drug development. Novel structures with high pharmacological activity are frequently found in marine organisms, which were previously not explored. This development is due to the high potential of modern analytical tools.^[1,2] New technologies for high-throughput screening, combined with automated NMR and mass spectroscopic analysis, allow for a faster assessment of the natural products.^[3] Still, the low quantities of substances available limit the structural characterization of these highly interesting molecules. Consequently, the structural information, gained by both MS and NMR spectroscopy, is invaluable for the elucidation of new chemical entities. The refinement of NMR techniques, not only by sophisticated 2D measurements but also simply by higher resolutions, that can be achieved with constantly less substance quantities ever increases the possibilities to gain structural information.^[2]

Polyketides are an important class of the above-mentioned natural products that are produced, although not ex-

clusively, by marine organisms. Especially the assignment of the stereochemistry of these molecules is an important part of structure elucidation. To date, still many polyketides are published “flat” despite the significance of stereogenic information for biological activity.^[4] The formation of single crystals for X-ray analysis is either difficult for the minuscule amounts or the substances are not solids, which is often the case for those molecules with a lower molecular weight. Therefore, the development of methods for the assignment of relative and absolute configurations by NMR spectroscopy is, besides asymmetric total synthesis, the most important source of information.^[5] In this context, we herein report a full account on a new method for the direct assignment of the relative configuration in 1,3-methyl-substituted alkyl chains (desoxypropionates), a structural feature abundantly present in polyketides (Figure 1).^[6] Furthermore, we demonstrate the reliability of our assignment method through the correct prediction of the relative configuration of the natural product xylarinic acid A and the confirmation of its absolute configuration by total synthesis. Finally, on the basis of this new NMR method, we propose the relative configurations of several previously unassigned polyketide natural products.

The NMR-based structure analysis of polyketides has been of interest for organic chemists in recent years. A variety of efforts was undertaken to elucidate not only the atom connectivity, but also the more intriguing and difficult to determine relative configuration of stereogenic centers. For 1,3-diols, the relative stereochemistry can be assigned by synthesis of the corresponding acetonide and determination of the characteristic ^{13}C chemical shift of the ketal carbon or by ^1H NMR measurement of OH/OD isotope shifts.^[7] On

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 Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201103988>.

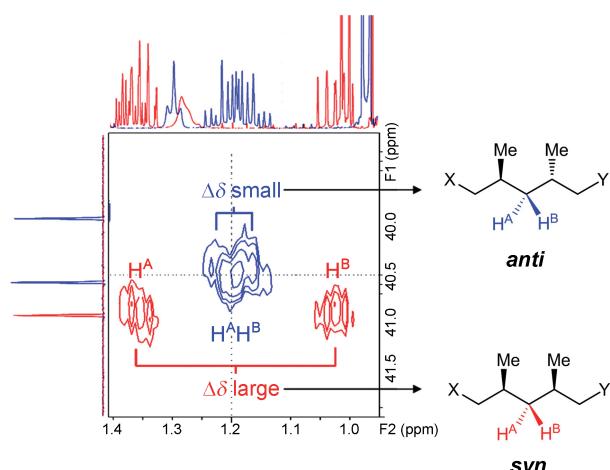


Figure 1. Assignment of the relative conformation in 1,3-methyl-substituted chains by using proton NMR spectroscopy.

the other hand, computational methods in combination with NMR measurements have been introduced, avoiding the necessity of chemical manipulation before analysis.^[5] Thus, Murata developed a method to determine the relative configuration in contiguous hydroxyl-containing propionates, based on $^{2,3}J_{\text{HC}}$ couplings.^[8] Additionally, structural information of polyketides can be obtained by the calculation of ^{13}C NMR chemical shifts and its comparison with the data obtained experimentally from natural material.^[9] Both of the methods require detailed conformational analyses and elaborate quantum mechanical calculations to achieve reliable predictions. Another approach proposed by Kishi, based on a universal NMR database, requires the prior syntheses of all diastereomers of an adequate model compound.^[10,11]

However, the very interesting polyketide structural motif of deoxypipronates still remains a challenge for structure determination. Hoffmann's approach of ^{13}C NMR calculations^[9] was used in some structure elucidations of desoxypropionate natural products. This method relies on the comparison of ^{13}C NMR data, obtained for the different diastereomers, with calculated spectra. Curran and Bajpai have recently shown, however, that different diastereomers of a natural product may show identical ^{13}C spectra.^[12] It proved to be more informative to compare the corresponding ^1H NMR spectra, because they provided significantly more reliable and distinguishable data for the examined diastereomers. Despite these restrictions, Hoffmann's method was used successfully in structure-determination efforts. The example of 4,6,8,10,16,18-hexamethyldocosane (**1**), a contact pheromone of the Australian sugarcane beetle, showcases the complexity of such an analysis (Figure 2). Kitching and

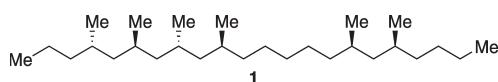


Figure 2. Desoxypipronate structure of 4,6,8,10,16,18-hexamethyldocosane (**1**).

co-workers used a multistep sequence to synthesize all possible diastereomers of this natural product in racemic form.^[13] By comparison of the thus obtained ^{13}C NMR data to the natural diastereomer, they found an exceptional *anti,anti,anti* relationship in the stereotetrad of the molecule and a more common *syn* relation between C16 and C18. The absolute configuration of the molecule was only recently determined by asymmetric total synthesis of all four remaining stereoisomers.^[14]

Over the last decade, our group has developed two independent methodologies for deoxypipronate synthesis. The first is based on a copper-mediated allylic substitution with Grignard reagents by employing *ortho*-diphenylphosphanyl benzoate as a directing leaving group.^[15] More recently, a second method was established that relies on a zinc-catalyzed enantiospecific sp^3 – sp^3 coupling.^[16] Both methodologies are perfectly suited to construct both *syn* and *anti* 1,3,*n*-methyl-branched hydrocarbon chains with perfect control of both relative and absolute configuration.

Alongside our synthetic efforts, we collected a multitude of NMR spectroscopic data for this type of desoxypipronate structures. It emerged as a rule for a specific molecule that the chemical-shift difference ($\Delta\delta$) for the methylene protons (H_A and H_B in Figure 1) varies significantly for the corresponding *syn* and *anti* compounds. As a model compound, *tert*-butylester **2** is shown in Figure 3.^[16] All four diastereomers are depicted with the methylene-proton section of their corresponding 2D-HSQC spectra (HSQC = heteronuclear single-quantum coherence). The hetero correlation spectrum is only necessary to correctly assign the position of the matching proton signals, especially in larger molecules. Comparison of the chemical shifts of these four isomers reveals obvious differences for *syn*- and *anti*-related diastereomers, for example, the AB signal in *syn,syn*-**2** and *anti,syn*-**2**. Obviously, the ^1H NMR of this type of 1,3-methyl-branched compounds exhibits distinct spectra for each diastereomer, an important prerequisite for a valid structure-assignment method.^[12,17]

To rationalize these findings, a conformational analysis for 1,3-dimethyl-substituted carbon chains is necessary. Thus, the preferentially populated conformations of such substructures are determined by the avoidance of *syn*-pentane interactions.^[9] Therefore, the only two conformers for *syn*- and *anti*-**3** free of *syn*-pentane interactions are the two depicted conformers *syn*- and *anti*-**3a/b**, respectively (Figure 4).

On analyzing the molecular environment of the methylene protons H_A and H_B , it turned out that these protons have a different local symmetry for the *syn* and *anti* diastereomers, respectively. This fact becomes evident when considering the case in which R equals R'. For this situation, the hydrogen atoms H_A and H_B in the diastereomers *anti*-**3a** and *anti*-**3b** are homotopic and thus, ^1H NMR chemical shifts are per definition the same. Conversely, for the diastereomers *syn*-**3a** and *syn*-**3b** these protons are diastereotopic and, owing to different chemical environments, have different chemical shifts in the ^1H NMR spectrum. For R ≠ R', the

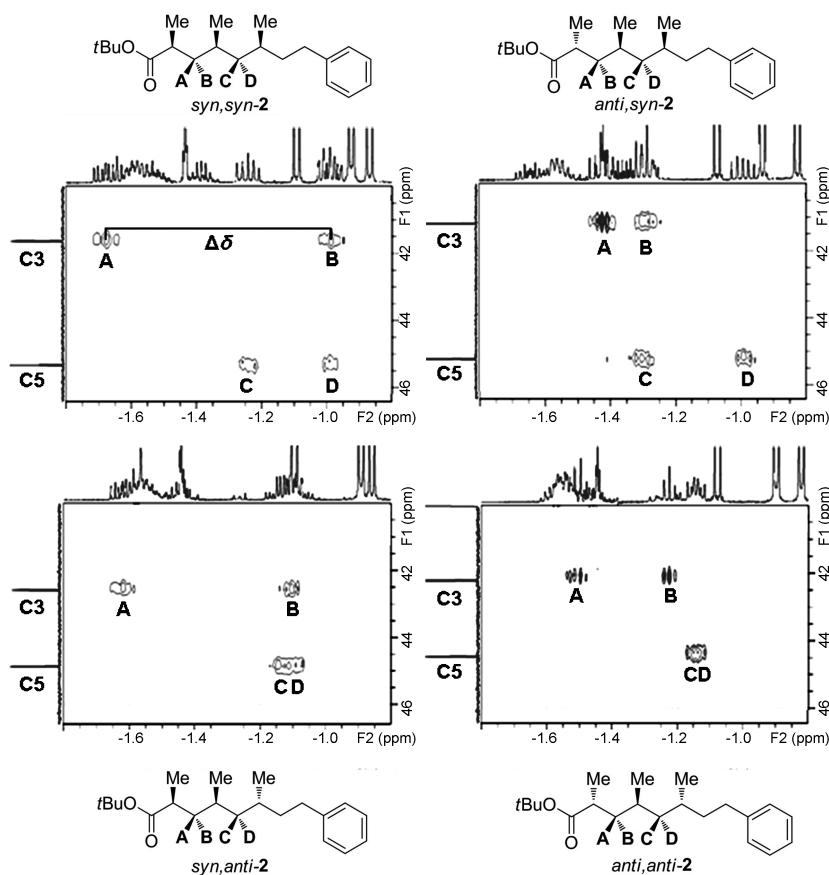
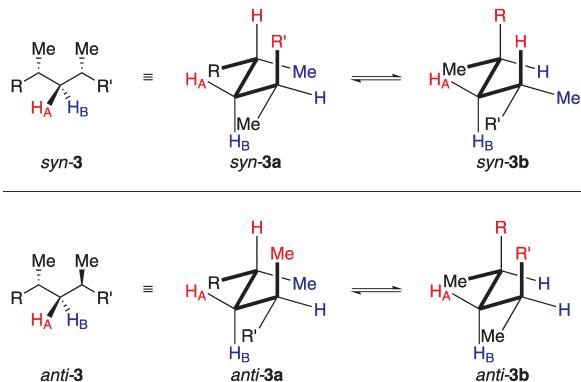


Figure 3. Comparison of the shift differences for all four diastereomers of ester 2.

Figure 4. Conformations of *syn* and *anti* deoxypropionates in a denoted diamond lattice.

global symmetry of the molecular objects is broken, however, this may have only a minor effect on the local symmetry situation for hydrogen atoms H_A and H_B . Consequently, for the *syn* diastereomer one expects large differences in chemical shift and smaller chemical-shift differences for the *anti* diastereomer in the ^1H NMR resonances of hydrogen atoms H_A and H_B .

Evidently, for the *syn*-related stereocenters the methylene protons differ notably in their chemical shift (Figure 3, sig-

nals A and B in *syn,syn*-2). The chemical shifts for the corresponding *anti* relationship exhibit a convergence of the signals (for *syn,syn*- vs. *anti,syn*-2) or an almost complete overlap of both signals (see signals C and D for *syn,syn*- vs. *syn,anti*-2). It is also evident that next to a carboxyl group (signals A and B) $\Delta\delta$ is very large for the *syn* compounds *syn,syn*- and *syn,anti*-2 and still observable in the *anti* compounds *anti,syn*- and *anti,anti*-2. Farther away from the functional group (signals C and D) in *syn,syn*- and *anti,syn*-2 $\Delta\delta$ is smaller than for the A/B signals, but in *anti,syn*- and *anti,anti*-2 $\Delta\delta$ diminishes to nearly zero.

Based on these initial findings, an extensive literature research was undertaken. We found more than 60 compounds with assigned ^1H NMR data (necessary for the $\Delta\delta$ analysis) and proven relative configuration. In this set of literature-known compounds, we could identify six pairs of matching *syn-anti* diastereomers. The cor-

responding differences in chemical shift for these *syn* and *anti* stereoisomers, together with another 11 examples synthesized in our lab, are compared in Figure 5. Thus, the effect is smallest in substances with an (unsubstituted) double bond adjacent to the 1,3-methyl substituents (**4–6**). Medium effects can be detected in alkyl-substituted chains with long distances to functional groups and in the case of hydroxy or chlorine substituents (**7–14**). A significant difference can be observed in proximity to carboxyl functions, such as esters (**15–18**) or amides (**19** and **20**). It is remarkable that even in the macrocycle of myxovirescin (**18**) the $\Delta\delta$ values show the same trend as in acyclic carbon chains. Additionally, the effect seems to be independent from neighboring stereogenic centers.

Together with the literature survey of 60 compounds and the data collected in our group, we analyzed the NMR data of more than 80 deoxypropionate natural products and synthetic intermediates (Figure 6). Most of the *anti*-configured substances exhibit $\Delta\delta$ values ranging from 0.0 to 0.2 ppm, whereas the majority of *syn* compounds exhibits $\Delta\delta$ values ranging from 0.2 to 0.5 ppm. The overlap region of both graphs (between 0.1 and 0.4 ppm) can be explained depending on the nature of the neighboring functional groups (compare Figure 5), as will subsequently be described in detail.

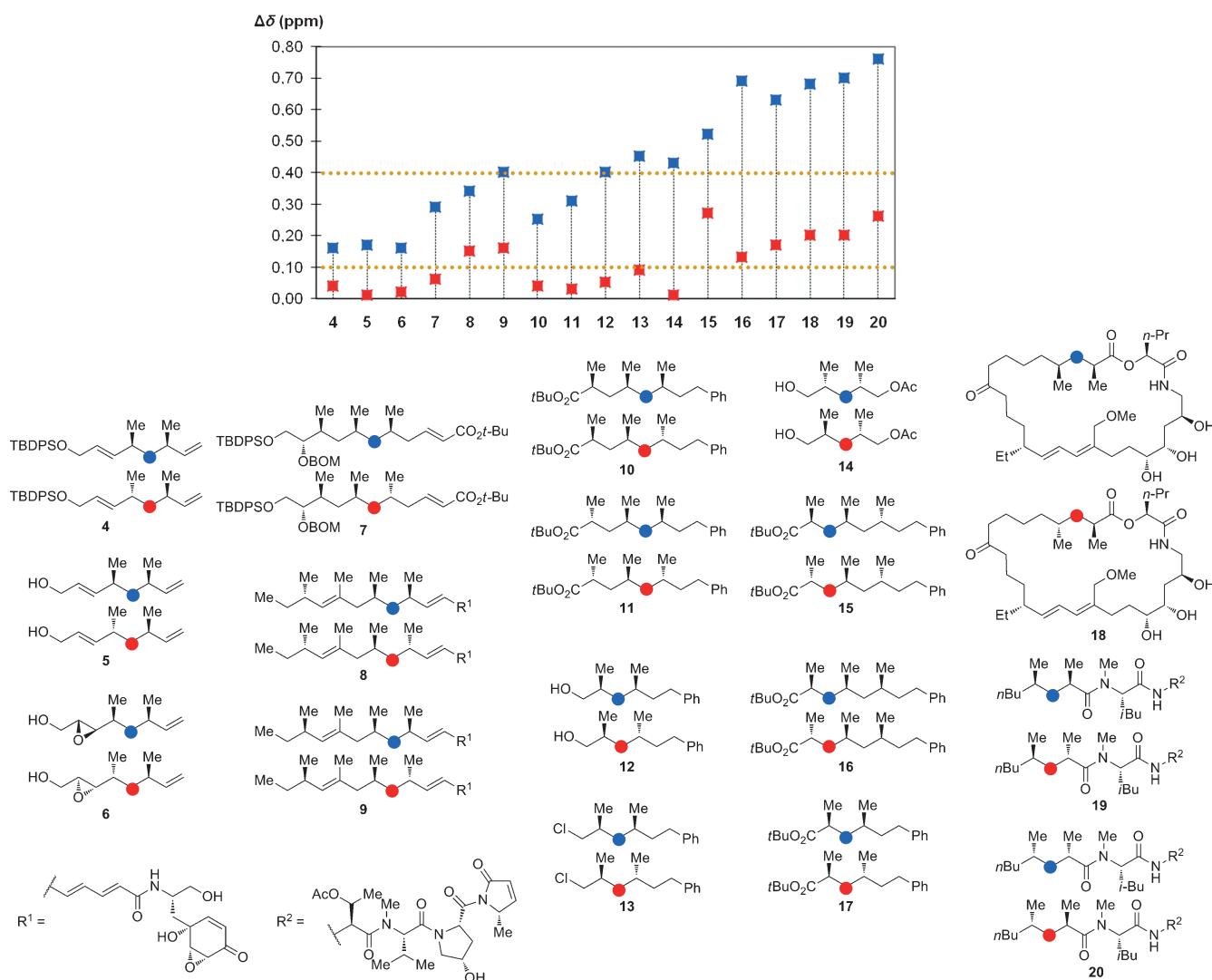


Figure 5. Direct comparison of corresponding *syn* and *anti* pairs. The graph displays the chemical-shift differences ($\Delta\delta$) for each compound (blue: *syn*, red: *anti*).

As mentioned previously, 4,6,8,10,16,18-hexamethyldocosane (**1**), a cuticular hydrocarbon of the cane beetle, is an excellent example for applying our assignment method (Figure 7). According to the $\Delta\delta$ values (corresponding to overlapping signals, compare Figure 3) shown for the stereotetrad, one would assign their unusual all-*anti* relationship by simple ^1H NMR analysis. Applying our method, we also would have predicted the *syn* configuration between C16 and C18, simply from analysis of the assigned ^1H NMR data reported.^[13] Compared to the immense synthetic work that was necessary beforehand, our method significantly improves available structure-elucidation techniques.

Despite the large scope of the method, which can even be applied in macrocycles, we also found limitations. In the natural product bitungolide A (**21**), the absolute configuration of which was unambiguously assigned by X-ray crystal-structure analysis, the $\Delta\delta$ value was found to be 0.57 ppm.^[18] In this structure, a chiral six-membered lactone is located directly adjacent to the 1,3-methyl branches, which certainly

influences the relative conformer equilibrium and, therefore, contradicts the presumed *syn* assignment.

According to our findings, the assignment of the relative configuration to a *syn* or *anti* compound can be accomplished by analysis of the shift difference ($\Delta\delta$) that is found for the methylene protons H_A and H_B, respectively. In general, in *anti* compounds smaller values for $\Delta\delta$ (<0.1 ppm) are observed compared to *syn* compounds (>0.4 ppm).^[6] However, the $\Delta\delta$ values are also dependent on neighboring functional groups and a comparison to known compounds is necessary if the $\Delta\delta$ values are in the medium range from 0.1 to 0.4 ppm (as depicted in Figures 5 and 6).

Selected examples of corresponding diastereomer pairs are shown in Figure 8. They demonstrate how the difference in chemical shift increases in the following order of substituents: carbon–carbon double bond < alkyl < alcohol or halogen < carbonyl or carboxyl (Figure 8). It was found that for a wide range of functional groups, *anti* compounds exhibit nearly no shift difference for the methylene protons. This

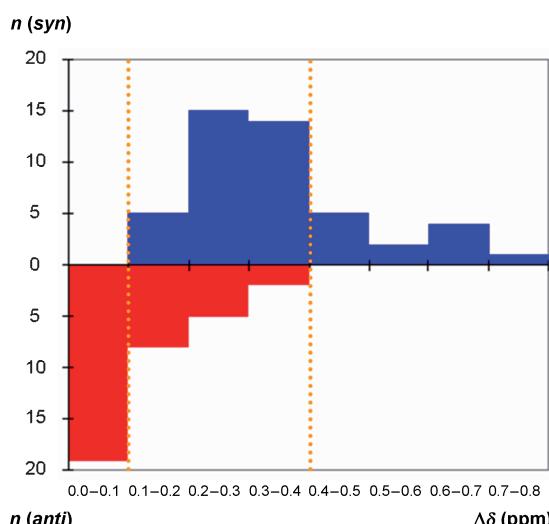


Figure 6. $\Delta\delta$ Values of literature-known compounds. The number of compounds is given for each 0.1 ppm range of $\Delta\delta$; *syn* compounds in blue, *anti* compounds in red.

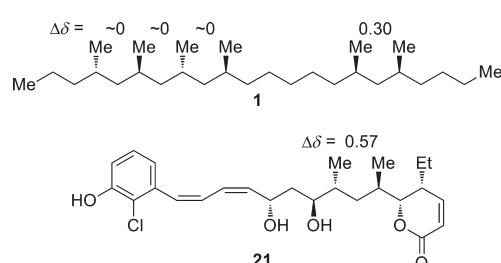


Figure 7. $\Delta\delta$ Values (ppm) of polypropionate natural products hexamethyldocosane (**1**) and bitungolide (**21**).

observation accounts for the simplified perception of rotationally symmetric surroundings of the two protons. On the other hand, for *syn*-configured compounds a gradually increasing shift difference was detected. Thus, the methylene protons are diastereotopic and the $\Delta\delta$ value depends on the shielding caused by the neighboring functional groups. In both cases, the $\Delta\delta$ values are largest next to a carbonyl function.

A complete survey of all data available exhibited the same tendencies as observed for the specific examples shown in Figure 8. The ranges of $\Delta\delta$ values obtained are given in Figure 9 according to the neighboring functional groups. Thus, the shift differences next to carbonyl groups (both ketones and carboxylic acid derivatives) are generally the largest, ranging from 0.1 up to 0.4 ppm for the *anti* compounds. In comparable *syn* compounds, the $\Delta\delta$ range shifts to values between 0.5 and 0.8 ppm. Molecules bearing an alcohol or halide next to the 1,3-dimethyl-substituted moiety exhibit $\Delta\delta$ ranges of 0.4 to 0.5 ppm (*syn*) and very small values of up to 0.05 ppm (*anti*). Also in alkyl-substituted compounds small *anti* $\Delta\delta$ values that range from about 0.0 to 0.1 ppm are observed, while the corresponding *syn* compounds have chemical-shift differences ranging from 0.2 to

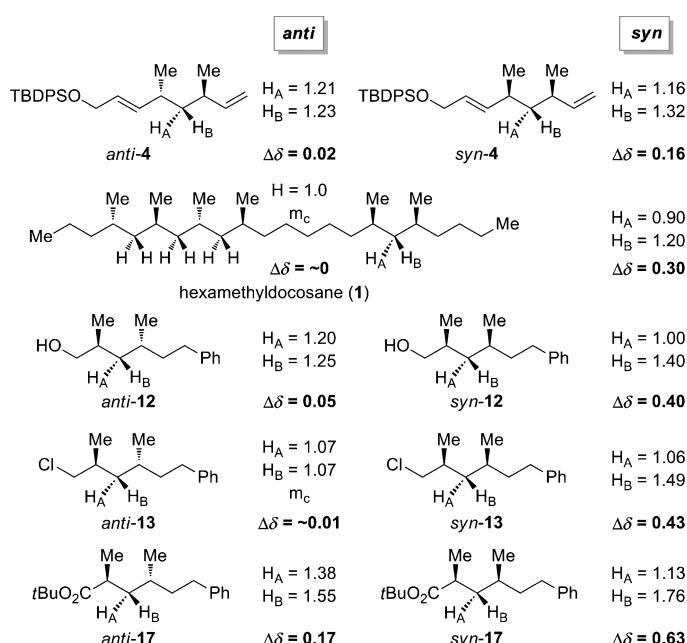


Figure 8. Exemplified range of $\Delta\delta$ values (ppm) for *syn* and *anti* compounds dependent on neighboring functional groups.

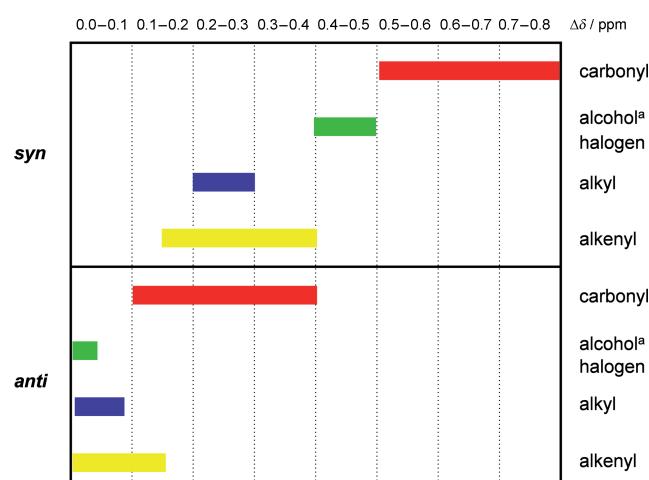


Figure 9. Tendencies for $\Delta\delta$ values dependent on functional groups (X and Y in Figure 1). a) Alcohols and related O-bound substituents.

0.3 ppm. Substances with C=C double-bond substituents again exhibit broader $\Delta\delta$ ranges from 0.0 to 0.15 ppm (*anti*) and from 0.15 to 0.4 ppm (*syn*). In this case, a possible ambiguity for an assignment of the relative configuration may arise just from the $\Delta\delta$ values. This is also owing to possible competition of the shielding effect, for example, when one substituent accounts for high $\Delta\delta$ values, while the other one causes a small $\Delta\delta$.

Such a borderline case is the carboxylic acid **22** (i.e., large $\Delta\delta$), having an additional phenyl substituent that should show a small $\Delta\delta$ value (Figure 10).^[19] While *anti*-**22** exhibited a shift difference of 0.37 ppm, the corresponding acid *syn*-**22** had only a slightly larger value of 0.44 ppm. Thus,

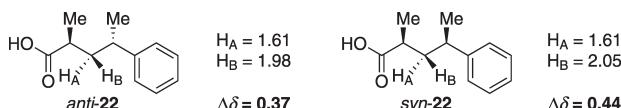


Figure 10. Comparison of the $\Delta\delta$ values (ppm) obtained for the carboxylic acids *anti*- and *syn*-22.

when assigning the relative configuration of unknown compounds, the sometimes contradicting influences of neighboring functional groups, as they are shown in Figure 10, have to be taken into account.

Our detailed analysis of literature data also revealed the influence of other stereogenic centers in the molecules on the corresponding shift differences (Figure 11). In the intermediate **7**, en route to a synthesis of borrelidin, the didesoxypyropionate moiety of the natural product is already present.^[20] Both *syn,syn*-**7** and *syn,anti*-**7** were synthesized and NMR analysis showed shift differences present not only for the ^{13}C signals of the methyl groups,^[9] but also different $\Delta\delta$ values for ^1H NMR signals of the methylene protons. It is

evident that the shift differences for the *syn* relation are consistent with expected values for oxygen substitution. However, the *anti* $\Delta\delta$ value of 0.16 ppm (*syn,anti*-**7**) is comparably large, accounting for the influence of the other stereocenters present. Thus, additional stereogenic centers may cause a larger difference in chemical shift for the methylene protons, also for an *anti* relationship of the 1,3-methyl groups. Again, the effect is stronger in proximity of a carbonyl functionality, as it is observed for microcolin (*syn*-**19**) and its epimer *anti*-**19**.^[21] In this case, asymmetric synthesis of four diastereomers was necessary to finally reveal the relative configuration of the natural product to be *syn*. The conjugate-addition product *anti*-**23** shows a similarly large $\Delta\delta$ value.^[22] Presumably, the rigid conformation of the oxazolidinone part of the molecule enhances the observed shift difference, a similar explanation may apply for the dithiane *anti*-**24**.^[23] Finally, the aryl-substituted carbonyl function in *anti*-**25** causes a $\Delta\delta$ value of 0.40 ppm.^[24] Here, the bulky aryl substituent is presumably twisted out of the plane of the carbonyl group and thus, strongly differentiates the electronic surroundings of the two methylene protons.

A very important feature of our method of direct assignment of relative configurations in desoxypolypropionate chains is that the effect proved to be independent from the solvent used for NMR measurements. Accordingly, the $\Delta\delta$ values of various natural products were examined together with the used deuterated solvents (Figure 12). The most common solvent for NMR measurements, CDCl_3 , was used with most of the intermediates we have shown so far. However, many natural products are not soluble in this rather nonpolar solvent and $[\text{D}_4]\text{MeOH}$, $[\text{D}_6]\text{DMSO}$, or even deuterated water are frequently necessary for the recording of NMR data. Therefore, a thorough knowledge of solvent influence on NMR shifts and solvent effects is crucial for structure elucidation. Interestingly, the analysis of NMR spectra of several natural products, recorded in a range of solvents with different polarities, revealed that the observed chemical-shift differences for *syn*- or *anti*-configured natural products (**26–29**) agree with the expected values for the corresponding functional groups depicted in Figure 9. Even with deuterated pyridine as the solvent, the $\Delta\delta$ value for atpenin B (**30**) is similar to that obtained for atpenin A5 (**25**) in $[\text{D}]\text{chloroform}$.

However, the assumption of the solvent having no influence on the $\Delta\delta$ values would not be valid without the measurement of a single pair of *syn* and *anti* diastereomers in different NMR solvents. Thus, we examined the ^1H NMR spectra of *syn*-**14** and *anti*-**14** in four deuterated solvents displaying different polarities (Table 1). Evidently, the $\Delta\delta$ values for *syn*-**14** only vary over a small range from 0.45 to 0.55 ppm for $[\text{D}]\text{chloroform}$, $[\text{D}_6]\text{benzene}$, $[\text{D}_6]\text{DMSO}$, and $[\text{D}_4]\text{MeOH}$. The shift differences for *anti*-**14** exhibit a similar range, but, in this case, the values are plainly in the expected region of *anti* compounds ranging from 0.09 to 0.15 ppm. This result emphasizes that a ^1H NMR-based assignment of relative configuration is not dependent on the deuterated solvent used in the experiment.

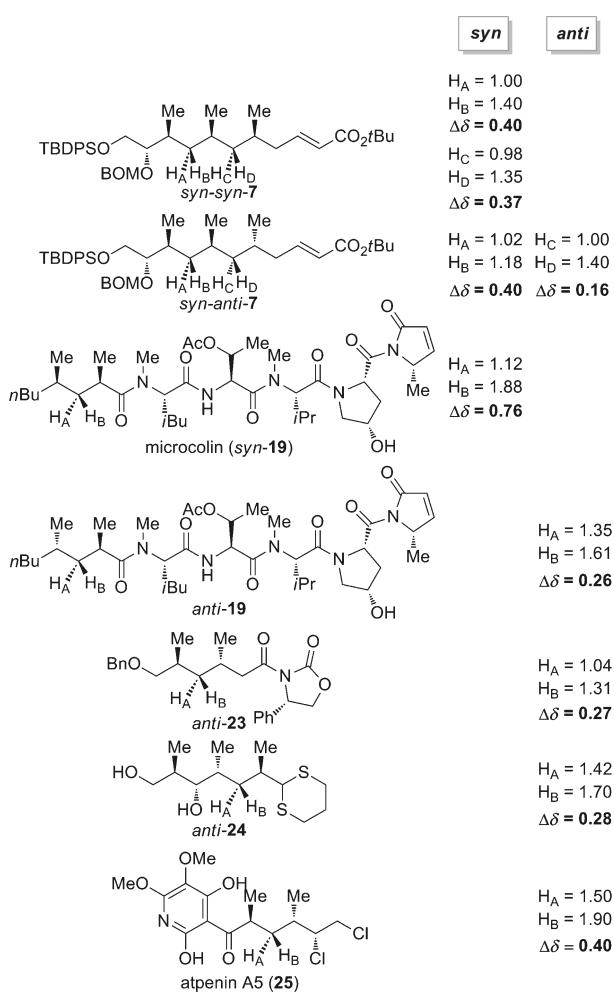


Figure 11. Influence of stereogenic centers on the observed methylene $\Delta\delta$ values (ppm).

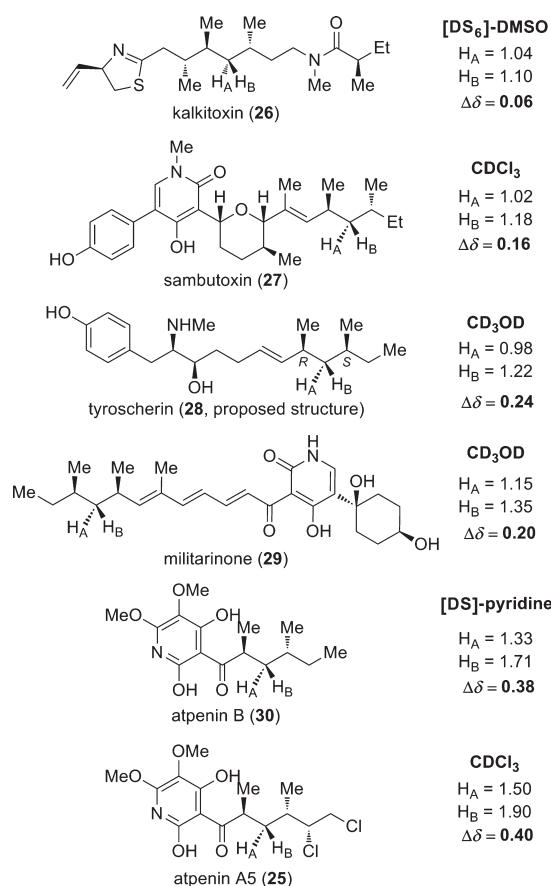


Figure 12. Observed $\Delta\delta$ values (ppm) for natural products in different deuterated solvents.

Table 1. Comparison of NMR chemical shifts of a *syn-anti* pair in various solvents.^[a]

Entry	Compound	CDCl ₃	C ₆ D ₆	[D ₆]DMSO	CD ₃ OD
1	HO-CH(Me)-CH(Me)-CO ₂ Et <i>syn-14</i>	0.45	0.55	0.48	0.48
2	HO-CH(Me)-CH(Me)-CO ₂ Et <i>anti-14</i>	0.09	0.11	0.15	0.13

[a] Chemical-shift differences ($\Delta\delta$) in ppm.

In the following, we describe several examples of structure determination and how desoxypropionate substructures had to be assigned previously. All examples use elaborate methods of spectroscopy combined with lengthy synthetic or computational efforts. In comparison, the same level of information can be achieved by following the assignment guidelines outlined above.

Assignment of the relative configurations of the natural products shown in Figure 12 was accomplished by using a number of complex analysis methods. Only the atpenins (**25** and **30**) were obtained as crystalline compounds. For the structure elucidation of kalkitoxin (**26**),^[25] the synthesis of elaborate fragments was necessary to assign the configura-

tion. In the case of sambutoxin (**27**),^[26] the final assignment was only possible by total synthesis.^[22] In the cases of tyroscherin (**28**)^[27] and militarinone (**29**),^[28] a synthetic effort could be evaded. For tyroscherin (**28**), degradation experiments lead to literature-known substances, which were compared by optical rotation and NMR spectroscopy.^[27] However, this method showed its limitations when the total synthesis of the proposed structure (*R,S*-isomer) resulted in NMR data different from natural material.^[29,30] While the proposed relative configuration of the 1,3-dimethyl substitution was correct, the relation to the amino alcohol moiety had to be revised.^[12] Unfortunately, NMR data of the revised structure of tyroscherin (i.e., *S,R*-isomer) were not assigned and 2D spectra were not available; therefore, the $\Delta\delta$ value could not be determined.^[30] Assignment of militarinone (**28**) was finally accomplished by using the universal NMR-database approach developed by Kishi.^[10,11,28] Similarly, to determine the relative configuration in scyphostatin (**31**), all four diastereomers of the highly elaborate model compound **32** were synthesized to compare the NMR data (Figure 13).^[31]

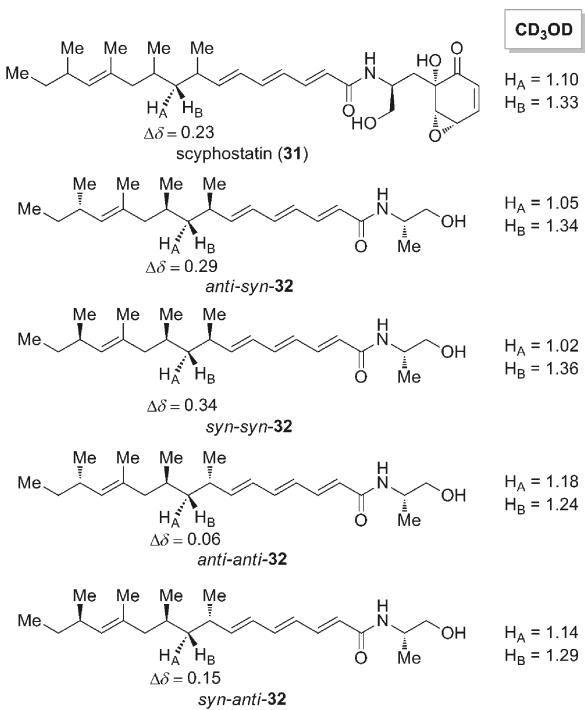


Figure 13. $\Delta\delta$ Values (ppm) of scyphostatin (**31**) and comparison with the diastereomers of model compound **32**.

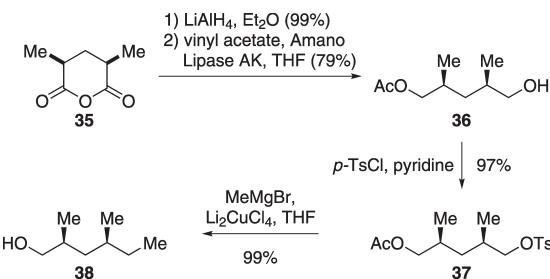
From our findings, we would have assigned the *syn* configuration for the $\Delta\delta$ value of 0.23 ppm with regard to the adjacent double bond, which is the same result as for the comparison with the diastereomers of compound **32**. The data for these four model compounds also show that the influence of neighboring stereogenic centers on the $\Delta\delta$ values is very little and our method is indeed applicable.

In the following, we intended to apply our new method on a natural product with unknown absolute and relative configuration. We were confident that we could correctly

predict the relationship of the methyl substituents in xylarinic acid A (**33**, Figure 14) and prove our assignment by asymmetric total synthesis. The polypropionates xylarinic acid A (**33**) and B (**34**) were isolated from the fungus *xylaria polymorpha* and exhibit strong antimycotic activity. The structure of both molecules was determined by analysis of NMR and mass spectrometric data, without a hint on the absolute or even relative configuration of the 1,3-methyl-substituted chain.^[32] Thorough examination of the NMR data published by Lee and co-workers provided the chemical-shift differences $\Delta\delta$ for the methylenic protons to be 0.22 ppm for the acid **33** and 0.21 ppm for the C₂-elongated derivative **34**. Compared to the data we had obtained for the *syn* and *anti* diastereomers of olefins **4**, **5**, and **6** (Figure 5), also containing a neighboring double bond, the *syn* configuration was predicted for both xylarinic acids A (**33**) and B (**34**).

To prove our assumption, we synthesized xylarinic acid A (**33**) in an asymmetric fashion. Our plan was to introduce the two stereogenic centers by an enzymatic desymmetrization, previously described by Fujita.^[33] Thus, our synthesis started with the commercially available *meso* anhydride **35** (Scheme 1). Ring opening with LiAlH₄ led to the *meso* diol in very high yield. This diol was then subjected to the enzymatic desymmetrization reaction. Amano lipase AK catalyzed the esterification with vinyl acetate to obtain the monoester **36** in good yield and very good enantiomeric purity (97.4% ee, determined by chiral HPLC of the corresponding tosylate **37**).^[33] The monoacetate **36** was then activated by using *para*-toluenesulfonic chloride in pyridine. Reaction with methylmagnesium bromide and Kochi's catalyst then accomplished both sp³–sp³ coupling and deprotection to give the free alcohol **38** in one step.

Subsequent Swern oxidation (Scheme 2) to the α -chiral aldehyde **39** was accomplished by careful workup at low temperature without racemization of the sensitive stereogenic center at C2.^[34] Horner–Wadsworth–Emmons olefination of the aldehyde **39** gave the α,β -unsaturated olefin **40**



Scheme 1. Asymmetric synthesis of alcohol **37** by using a desymmetrizing key step.

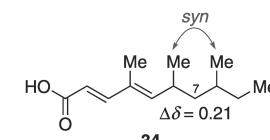
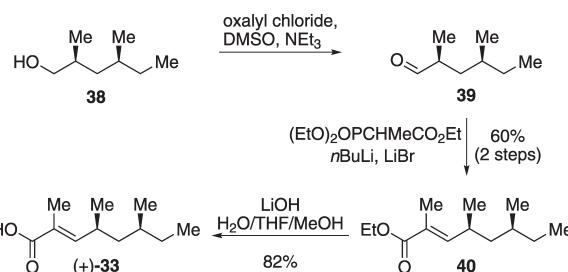


Figure 14. Structures of xylarinic acids A (**33**) and B (**34**); chemical-shift differences ($\Delta\delta$) are given in ppm.



Scheme 2. Synthesis of the predicted structure (*syn*-**33**) of xylarinic acid A.

with an *E/Z* selectivity of 85:15.^[35] Chromatographic separation of the undesired isomer provided the pure *E* isomer of **40** in 60% yield over the two steps. Finally, saponification of the ester with lithium hydroxide gave the target molecule (+)-**33** in good yield.

Recording of the NMR spectroscopical data and comparison with those data obtained from natural material, which was published by Yun and co-workers, showed a complete match of both data sets. Therefore, we correctly assigned the relative configuration to be *syn* for xylarinic acid A by analysis of its published ¹H NMR data. However, when we compared the optical rotatory power of the synthetic material (+51.7°, *c*=1.0, MeOH), we found that (+)-**33** had to be the enantiomer of the natural product (-25.0°, *c*=0.1, MeOH).^[32] Thus, we assigned the absolute configuration of the natural product to be *S,S*-**33**, as it is depicted in Figure 15.

With the accomplishment of the asymmetric total synthesis of *ent*-xylarinic acid A, we were able to proof the validity of our ¹H NMR-based structure-determination method. Thus, it is now possible to predict the relative configurations for a wide range of natural products bearing desoxypropionate moieties. In the following, we propose the relative configurations of several natural products with to date unassigned 1,3-dimethyl-branched substructures.

Machillene (**41**), a cytotoxic compound isolated from the stem wood of the Taiwanese evergreen tree *machilus zuihoensis* Hyata, was shown to be a chiral bisepoxide, as depicted in Figure 16.^[36] Its relative configuration on the epoxides was deduced from the absence of NOE contacts between the protons at C1/2 and C10/11. There was no NMR chemical-shift difference found for the two methylene protons at C6 ($\Delta\delta=0$ ppm). Therefore, based on our method,

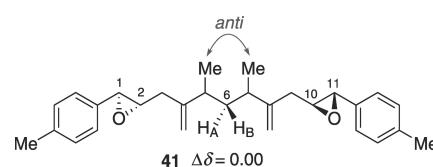


Figure 16. Structure of machillene (**41**) and proposed configuration based on the published NMR data ($\Delta\delta$ in ppm).^[36]

this strongly suggests an *anti* relationship for the methyl groups. In this case, the assumption is highly valid, because the bisepoxide **41** is a symmetrical compound and, as such, represents a textbook example for our simplified model (compare Figure 4), rendering the methylene protons homotopic.

The structure of cryptosphaerolide (**42**, Figure 17) was determined by the usual combination of chemical derivatiza-

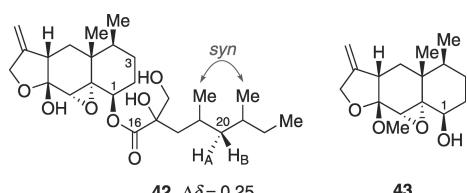


Figure 17. Structure of cryptosphaerolide (**42**) and proposed configuration based on the published NMR data and biologically inactive derivative **43** ($\Delta\delta$ in ppm).^[36]

tion and spectroscopic methods.^[37] Additionally, compound **42** exhibited potent activity against colon cancer cell lines. For their studies, Oh and co-workers planned to use the Mosher ester method for derivatization to elucidate the conformation of the tricyclic substructure. During the synthesis, the group obtained compound **43** after methyl acetal formation and ester hydrolysis. Interestingly, without the side chain in place, the compound lost all biological activity, thus, suggesting an important role of the propionate moiety for the inhibition mechanism.

Starting from the alcohol **43**, it was possible to determine the absolute configuration of the alcohol at C1 and also, by NOESY correlation measurement, the complete configuration of the molecule on the tricyclic ring system. By using our method, the relative configuration of the two methyl groups in the side chain can now additionally be assigned. The $\Delta\delta$ value for the C20 protons was found to be 0.25 ppm, which correlates to a *syn* compound if we take into account the alkyl substituent on one side and the oxygenated residue on the other side of the stereodiad (compare Figure 9).

Another natural product of polyketide origin, penicidite A (**44**, Figure 18), exhibited moderate cytotoxic activity against the human hepatocellular liver carcinoma cell line.^[38] In this case, the relative configuration on the six-membered ring was again determined by using NOESY measurements. Additionally, the absolute configuration of the isolated alcohol at C15 was determined to be *R* by Mosher ester derivatization. Also for this structure, the dif-

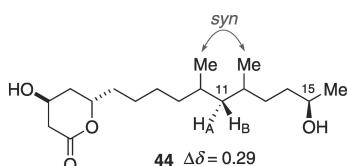


Figure 18. Structure of penicidite A (**44**) and proposed configuration based on the published NMR data ($\Delta\delta$ in ppm).^[38]

ference in chemical shift for the C11 protons ($\Delta\delta = 0.29$ ppm) suggests a relative *syn* configuration.

Finally, the structure of the electron-transport-enzyme inhibitor paecilaminol (**45**) was determined without any information about the relative configuration of the four stereogenic centers.^[39] However, our method reveals a *syn* relationship for the only alkyl-group-substituted stereodiad at C15 (Figure 19).

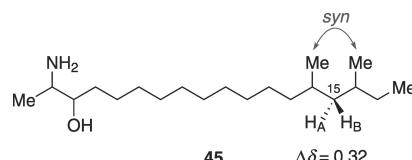


Figure 19. Structure of paecilaminol (**45**) and proposed configuration based on the published NMR data ($\Delta\delta$ in ppm).^[39]

Conclusion

In this full account on a ^1H NMR-based assignment method for the relative configuration of 1,3,*n*-methyl-branched carbon chains, we have shown that our method is valid for a broad range of natural products. Additionally, assignments were possible in a variety of deuterated solvents, because the corresponding shift differences were not significantly influenced by the solvent. The $\Delta\delta$ values found were dependent on both neighboring functional groups and/or stereogenic centers. However, it was possible to assign the relative configuration of an unknown compound according to the functional groups attached, when the determined values are compared with (in a broader sense) similarly substituted compounds. For this purpose, we derived an empiric rule for the ranges in which $\Delta\delta$ values usually occur (compare Figure 9). Furthermore, we were able to demonstrate the value of our method by successful prediction of the relative configuration of the polyketide natural product xylarinic acid A (**33**) and asymmetric total synthesis of its enantiomer *ent*-**33**. Finally, we were able to predict the relative configurations of 1,3-methyl-substituted subunits in several natural products. These predictions were possible based on the simple analysis of published ^1H NMR data and determination of the chemical-shift differences of the relevant methylene protons. The presented method broadens the toolset of the analytical chemist without the need for more material or even the conduction of specially designed experiments. Thus, we hope that our approach will supersede many of the tedious synthetic efforts necessary to date and that it will simplify the structure elucidation of polyketide natural products in the future.

Experimental Section

General remarks: All reactions were carried out under an atmosphere of argon 5.0 (Südwest-Gas) in dried glassware. Air- and moisture-sensitive liquids and solutions were transferred by using a syringe. All solvents

were dried and distilled by using standard procedures. Solutions were concentrated under reduced pressure by rotary evaporation. Chromatographic purification of products was accomplished on Merck silica gel Si 60 Å (200–400 mesh). Nuclear magnetic resonance spectra were acquired on a Varian Mercury spectrometer (300 MHz and 75 MHz for ¹H and ¹³C, respectively) and on a Bruker AMX 400 (400 MHz and 101 MHz for ¹H and ¹³C, respectively) and were referenced according to internal TMS standard or solvent signals (CDCl₃: δ = 7.26 ppm; C₆D₆: δ = 7.16 ppm). Data for ¹H NMR spectra are reported as follows: chemical shift (δ in ppm), multiplicity (s: singlet, brs: broad singlet, d: doublet, t: triplet, q: quartet, m: centered multiplet, m: multiplet), coupling constant (Hz), integration. Data for ¹³C NMR spectroscopy are reported in chemical shift (δ in ppm). The E/Z ratio was determined by NMR analysis. Assignment of the ¹H NMR resonances was accomplished by H,H-COSY-NMR experiments and for ¹³C NMR spectroscopy by C,H-COSY-NMR experiments.

(2R,4S)-2,4-dimethylpentane-1,5-diol: The *meso* anhydride **35** was synthesized following a literature procedure.^[40] A suspension of **35** (100 mmol, 14.3 g, 1.00 equiv) in diethyl ether (300 mL) was cooled to 0°C. Lithium aluminium hydride (200 mmol, 7.59 g, 2.00 equiv) was added stepwise under vigorous stirring over 1 h. The suspension was allowed to warm to room temperature overnight. The reaction mixture was cooled again to 0°C and water (8 mL), an aqueous solution of sodium hydroxide (15%, 8 mL), diethyl ether (100 mL), and water (24 mL) were added successively. The reaction mixture was stirred until its color turned from grey to white (about 2 h) and dried over sodium sulfate. The solvent was removed in vacuo to obtain the title compound as a colorless, viscous, and hygroscopic oil (13.0 g, 99%). ¹H NMR (400 MHz, CDCl₃): δ = 0.94 (ddd, J = 14.2, 7.1, 7.1 Hz, 1H), 0.95 (d, J = 6.7 Hz, 6H), 1.53 (ddd, J = 13.7, 6.8, 6.8 Hz, 1H), 1.74 (ddqdd, J = 7.0, 6.8, 6.7, 5.7, 5.7 Hz, 2H), 1.87 (brs, 2H), 3.48 ppm (d, J = 5.7 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃): δ = 17.6 (2C), 33.1 (2C), 37.0, 67.9 ppm (2C). The spectroscopic data match with those reported in the literature.^[41]

(2S,4R)-5-hydroxy-2,4-dimethylpentyl acetate (36): A solution of (2R,4S)-2,4-dimethylpentane-1,5-diol (2.00 g, 15.1 mmol, 1.00 equiv) in tetrahydrofuran (20 mL) was cooled to 0°C. At this temperature, amano lipase AK (110 mg) and vinyl acetate (2.10 mL, 1.95 g, 22.7 mmol, 1.50 equiv) were added. The reaction mixture was stirred for 30 min at 0°C and for 7 h at 5°C. The enzyme was removed by suction-filtration through Celite and washed with diethyl ether (40 mL). The homogeneous filtrate was concentrated in vacuo. Purification by flash chromatography (diethyl ether, Ø 5 cm, length 16 cm, fraction size 40 mL, fractions 9–16) yielded the title compound as a colorless oil (2.09 g, 79%). [α]_D²⁴ = +11.42 (c = 1.05, CHCl₃, 97% ee); ¹H NMR (400 MHz, CDCl₃): δ = 0.95 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 1.00 (ddd, J = 13.8, 7.7, 7.1 Hz, 1H), 1.45 (ddd, J = 13.7, 7.1, 6.6 Hz, 1H), 1.52 (brs, 1H), 1.74 (ddqdd, J = 7.7, 7.1, 6.7, 6.6, 5.5 Hz, 1H), 1.90 (ddqdd, J = 7.1, 6.8, 6.7, 6.6, 5.4 Hz, 1H), 2.06 (s, 3H), 3.41 (dd, J = 10.3, 6.6 Hz, 1H), 3.50 (dd, J = 10.3, 6.6 Hz, 1H), 3.85 (dd, J = 10.8, 6.8 Hz, 1H), 3.97 ppm (dd, J = 10.8, 5.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 17.2, 17.8, 20.9, 30.0, 33.0, 37.3, 68.0, 69.2, 171.3 ppm. The spectroscopic data match with those reported in the literature.^[42]

(2S,4R)-2,4-dimethyl-5-(tosyloxy)pentyl acetate (37): A solution of monoacetate (**36**) (1.70 g, 9.76 mmol, 1.00 equiv) in dry pyridine (30 mL) was cooled to 0°C. Then *p*-toluenesulfonyl chloride (2.79 g, 14.6 mmol, 1.50 equiv) was added stepwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched by the addition of water (50 mL), followed by extraction with diethyl ether (3 × 40 mL). The combined organic layers were washed with a saturated solution of copper(II)sulfate (2 × 60 mL), a saturated solution of sodium hydrogen carbonate (30 mL), and brine (30 mL). The organic phase was dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography (cyclohexane/ethyl acetate 1:1, Ø 5 cm, length 18 cm, fraction size 40 mL, fractions 7–10) yielded the title compound as a colorless oil (3.10 g, 97%, 97% ee). [α]_D²⁴ = +1.61 (c = 1.24, CHCl₃, 97% ee); HPLC (Daicel Chiracel OJ-H column, heptane/ethanol 75:25, flow rate = 0.8 mL min⁻¹, 23°C, detection at λ = 230 nm): *t*₁ = 15.37 min (major), *t*₂ = 20.83 min (minor); ¹H NMR (400 MHz, CDCl₃):

δ = 0.90 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 1.00 (ddd, J = 13.9, 7.4, 7.4 Hz, 1H), 1.39 (ddd, J = 13.8, 6.9, 6.9 Hz, 1H), 1.79 (dqddd, J = 7.4, 6.8, 6.8, 6.8 Hz, 1H), 1.89 (qddd, J = 6.7, 6.7, 6.7, 5.4 Hz, 1H), 2.04 (s, 3H), 2.45 (s, 3H), 3.79 (dd, J = 10.8, 6.5 Hz, 1H), 3.80 (dd, J = 9.5, 6.2 Hz, 1H), 3.87 (dd, J = 10.7, 5.4 Hz, 1H), 3.88 (dd, J = 10.6, 5.3 Hz, 1H), 7.33–7.37 (m, 2H), 7.76–7.81 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ = 17.1, 17.4, 20.9, 21.6, 29.8, 30.3, 36.9, 68.8, 74.7, 127.8 (2C), 129.8 (2C), 133.1, 144.7, 171.1 ppm. The spectroscopic data match with those reported in the literature.^[43]

(2S,4S)-2,4-dimethylhexan-1-ol (38): Lithium chloride (424 mg, 10.0 mmol, 1.00 equiv) and copper(II)chloride (672 mg, 5.00 mmol, 0.50 equiv) were flame dried in a flask and dissolved in tetrahydrofuran (50 mL) to obtain an orange solution of lithium tetrachlorocuprate(II) (0.1 M in tetrahydrofuran). A solution of the tosylate **37** (3.30 g, 10.0 mmol, 1.00 equiv) in tetrahydrofuran (100 mL) was cooled to -78°C. The solution of lithium tetrachlorocuprate(II) (0.1 M in tetrahydrofuran, 50 mL, 5.0 mmol, 0.50 equiv) was added by using a syringe. After 10 min, a solution of methylmagnesium bromide (3.0 M in diethyl ether, 17 mL, 25 mmol, 5.0 equiv) was added by using a cannula. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled to 0°C and quenched by the addition of water (0.7 mL), an aqueous solution of sodium hydroxide (10%, 0.7 mL), and water (0.7 mL). The suspension was dried over sodium sulfate, filtered by suction-filtration over Celite, and concentrated in vacuo. Purification by distillation (30 mbar, 80°C) or alternatively by flash chromatography (petroleum ether/diethyl ether 1:1, Ø 5 cm, length 18 cm, fraction size 25 mL, fractions 8–12) yielded the title compound as a colorless oil (1.29 g, 99%). [α]_D²⁴ = -3.3 (c = 1.85, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ = 0.86 (t, J = 7.4 Hz, 3H; H-6), 0.88 (d, J = 6.6 Hz, 3H; 4-CH₃), 0.92 (d, J = 6.7 Hz, 3H; 2-CH₃), 0.89–0.98 (m, 1H; H-5), 1.02–1.15 (m, 1H; H-3), 1.26–1.48 (m, 3H; H-3, H-5, H-4), 1.51 (brs, 1H; 1-OH), 1.65–1.76 (m, 1H; H-2), 3.37 (dd, J = 10.5, 6.8 Hz, 1H; H-1), 3.52 ppm (dd, J = 10.5, 5.2 Hz, 1H; H-1); ¹³C NMR (100 MHz, CDCl₃): δ = 11.1 (C-6), 17.3 (2-CH₃), 19.8 (4-CH₃), 29.0 (C-5), 31.6 (C-4), 33.1 (C-2), 40.6 (C-3), 68.4 ppm (C-1); MS (CI (NH₃), C₈H₁₈O, exact mass = 130.1): m/z (%) = 70.2 (18), 83.2 (52), 112.1 (29), 148.1 (100); HRMS (CI (NH₃)): m/z calcd for C₈H₂₂ON: 148.1701 [M+NH₄]⁺; found: 148.1698. The spectroscopic data match with those reported in the literature.^[44]

E-(4S,6S)-Ethyl-2,4,6-trimethyloct-2-enoate (40): A solution of oxalyl chloride (0.18 mL, 0.27 g, 2.1 mmol, 1.4 equiv) in dichloromethane (4 mL) was cooled to -78°C and DMSO (0.27 mL, 0.30 g, 3.8 mmol, 2.6 equiv) was added. After stirring at this temperature for 15 min, a solution of alcohol **38** (193 mg, 1.48 mmol) in dichloromethane (2 mL) was added and the mixture was stirred at -78°C for 1 h. Then, triethylamine (1.0 mL, 0.73 g, 7.2 mmol, 4.9 equiv) was added to the reaction mixture and the reaction was warmed to 0°C and stirred for 1 h at this temperature. The reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl (10 mL) and extracted with diethylether/n-pentane (4:1, 3 × 10 mL). The combined organic phases were dried over Na₂SO₄ and the solvents were evaporated in vacuo (max. 200 mbar) at 0°C. The thus obtained crude aldehyde **39** was directly used without further purification.^[45] A solution of LiBr (260 mg, 2.99 mmol, 2.02 equiv) in acetonitrile (10 mL) was stirred for 10 min at room temperature, then triethyl 2-phosphonopropionate (0.64 mL, 0.70 g, 3.0 equiv) was added. After additional 10 min of stirring at room temperature, the mixture was cooled to 0°C and *n*-butyllithium (2.24 M in hexane, 1.0 mL, 2.24 mmol, 1.51 equiv) was added dropwise. After 1 h stirring at 0°C, a solution of the crude aldehyde **39** in acetonitrile (2 mL) was added and the reaction mixture was stirred at 0°C overnight. The reaction was quenched by the addition of a saturated aqueous solution of NH₄Cl (20 mL) and extracted with diethylether (3 × 15 mL). The combined organic phases were dried over Na₂SO₄ and the solvents were evaporated in vacuo. Purification of the residue by silica gel chromatography gave the title compound **40** (135 mg, E/Z = 65:35, 189 mg pure E isomer, 60%, E/Z_{total} = 85:15) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 0.83 (d, ³J = 6.3 Hz, 3H; 6-CH₃), 0.85 (t, ³J = 7.0 Hz, 3H; 8-H), 0.98 (d, ³J = 6.6 Hz, 3H; 4-CH₃), 1.09–1.18 (m, 2H; 5-H_A, 7-H_A), 1.21–1.39 (m, 3H; 5-H_B, 6-H, 7-H_B), 1.30 (t, ³J = 7.1 Hz, 3H, 2'-H), 1.85 (d, ⁴J = 1.5 Hz, 3H; 2-CH₃), 2.61 (m, 1H; 4-H), 4.19 (q, ³J = 7.1 Hz, 2H; 1'-H), 6.50 ppm (dq, ³J = 10.2 Hz, ⁴J =

1.4 Hz, 1 H; 3-H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 11.3$ (C-8), 12.5 (2- CH_3), 14.4 (C-2'), 19.1 (6- CH_3), 20.6 (4- CH_3), 30.1 (C-7), 31.0 (C-4), 32.4 (C-6), 44.3 (C-5), 60.5 (C-1'), 126.2 (C-2), 148.4 (C-3), 168.6 ppm (C-1). The spectroscopic data match those reported in the literature.^[46]

E-(4S,6S)-Ethyl-2,4,6-trimethyloct-2-enoic acid (33): A solution of LiOH· H_2O (287 mg, 6.84 mmol, 10.2 equiv) in water (2.5 mL) was added to a solution of ester **40** (143 mg, 0.673 mmol) in methanol (0.7 mL) and tetrahydrofuran (1.3 mL) at room temperature. The reaction mixture was stirred overnight and then an aqueous solution of HCl (2 M) was added until pH 1 was detected. The aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic phases were dried over MgSO_4 and the solvents were evaporated in vacuo. Purification of the residue by silica gel chromatography gave the title compound **33** (102 mg, 82 %) as a colorless oil. $[\alpha]_D^{24} = +64.9^\circ$ ($c = 1.12, \text{CHCl}_3$); $[\alpha]_D^{24} = +51.7^\circ$ ($c = 1.00, \text{MeOH}$); ^1H NMR (400 MHz, CDCl_3): $\delta = 0.83$ (d, $^3J = 6.3$ Hz, 3 H; 6- CH_3), 0.85 (t, $^3J = 7.3$ Hz, 3 H; 8-H), 1.00 (d, $^3J = 6.7$ Hz, 3 H; 4- CH_3), 1.10–1.19 (m, 2 H; 5-H_A, 7-H_A), 1.20–1.35 (m, 2 H; 6-H, 7-H_B), 1.37 (ddd, $^2J = 12.2$ Hz, $^3J = 8.5$, 4.0 Hz, 1 H; 5-H_B), 1.86 (d, $^4J = 1.4$ Hz, 3 H; 2- CH_3), 2.63 (m, 1 H; 4-H), 6.66 ppm (dq, $^3J = 10.2$ Hz, $^4J = 1.4$ Hz, 1 H; 3-H); ^{13}C NMR (101 MHz, CDCl_3): $\delta = 11.3$ (C-8), 12.2 (2- CH_3), 19.1 (6- CH_3), 20.5 (4- CH_3), 30.1 (C-7), 31.2 (C-4), 32.5 (C-6), 44.1 (C-5), 125.5 (C-2), 151.3 (C-3), 173.6 ppm (C-1). The spectroscopic data match those reported in the literature.^[32]

Acknowledgements

This work was supported by the DFG, the International Research Training Group “Catalysts and Catalytic Reactions for Organic Synthesis” (IRTG 1038) and the Fonds der Chemischen Industrie (Fellowship to Y.S.).

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Received: December 12, 2011

Published online: April 27, 2012