syn/anti-Configurational Assignment of *sec*-Butylcarbinols Based on ^{13}C-NMR Spectra

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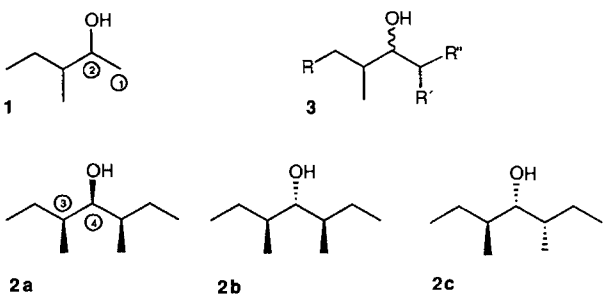
syn or *anti* configuration[1] can be assigned to the diastereomers of the *sec*-butylcarbinols **3** by analysis of diagnostic differences in the ^{13}C-NMR spectra. Likewise, the ^{13}C-NMR shifts of the diastereotopic methyl groups in isopropylcarbinols of type **19** have been assigned.

The assignment of the relative configuration in compounds having adjacent stereocenters is a recurring problem in the structural elucidation of natural products and of intermediates generated in the course of stereoselective transformations. When dealing with conformationally defined cyclic six-membered rings, ^{1}H- and ^{13}C-NMR spectroscopy serves well to establish the equatorial or axial disposition of a substituent. While in open-chain structures the same effects should be observable, they are generally leveled by a rapid equilibration between a multitude of local conformations. In order to establish the realtive configuration of open-chain structures, one is therefore frequently forced to convert the compounds of interest into conformationally rigid derivatives, before the NMR spectra can be analysed[2]. However, some classes of compounds such as 1,3-diols[2], γ-hydroxy amines[3], γ-hydroxy ethers[4] or β-hydroxy ketones[5] exist frequently in internally hydrogen-bonded conformations, allowing direct assignment of the relative configurations based on the ^{13}C-NMR spectra. For all other conformationally mobile systems a correlation of ^{13}C-NMR data with the relative configuration is possible only after population analysis of all low-energy conformers, and a prediction of the ^{13}C-NMR chemical shifts based on a weighted average of the conformers[6,7]. But even this approach has its limitations, since the observed differences in the ^{13}C-NMR chemical shifts for diastereomers may be too small for a meaningful interpretation, e.g. the ^{13}C-NMR spectra of the diastereomers of **1** differ only by 0.3 ppm for C-2 and 1.0 ppm for C-1.

Scheme 1



Fortunately, the analysis becomes easier in more highly substituted systems, because the number of low-energy conformers to be considered gets smaller. Thus, it was pointed out in an earlier paper[8] that for each of the diastereomeric compounds **2** only two low-energy conformations around the C-3/C-4 bond are available. Based on the assumption that these two local conformations are equally populated, the diagnostic differences in the ^{13}C-NMR chemical shifts of **2a**, **2b** and **2c** could be interpreted[8]. Meanwhile, we have access to a larger set of ^{13}C-NMR data of *sec*-butylcarbinols. From this it can be shown that the effects reported for the diastereomers of **2** are general and can be used to assign the *syn* and *anti* configurations[1] of partial structures such as **3**.

Assignment of Relative Configuration of *sec*-Butylcarbinols

Table 1 contains the ^{13}C-NMR shift data for a set of *syn*- and *anti*-*sec*-butylcarbinols, the structures of which have been independently secured by chemical correlation methods. It is obvious that the chemical shift of the methyl group is shifted downfield by +3.0 ppm on going from the *syn* to the *anti* diastereomer[1]. The signal of the "in chain" secondary carbon is in turn shifted upfield by −3 ppm when going from the *syn* to the *anti* diastereomer.

These findings are fully in line with the predictions made in the earlier paper[8]. These predictions are based on the assumption that the *syn* isomer of **3** should populate only the two conformations **4a** and **4b**, the *anti* isomer of **3** only the conformations **5a** and **5b**. Any other local conformation should have destabilizing g^+g^--interactions[13], equivalent to 1,3-diaxial interactions between non-hydrogen substituents on a six-membered ring. These other conformations can therefore be neglected. With reference to substituent effects in rigid *trans*-decalin structures, the chemical shifts shown may be predicted for each conformer[8].

Assuming that the conformations **a** and **b** are populated to the same extent, the average chemical shifts for the *syn* isomer come out to δ = 27.15 and 14.85, and for the *anti*

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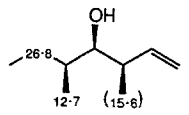
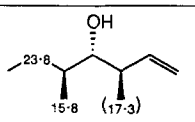
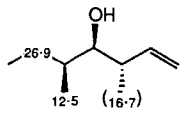
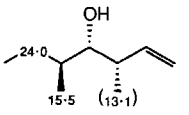
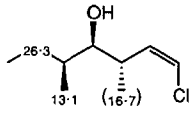
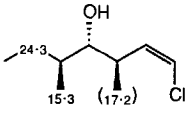
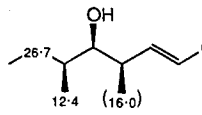
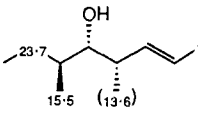
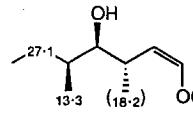
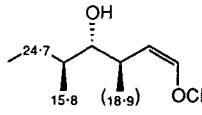
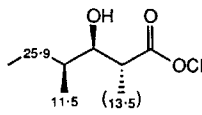
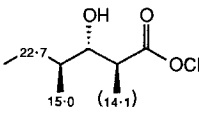
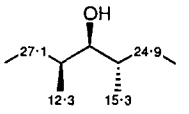
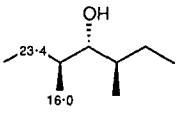
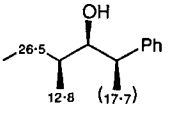
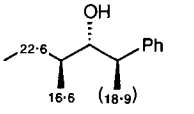
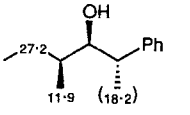
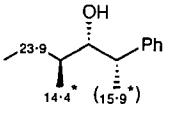
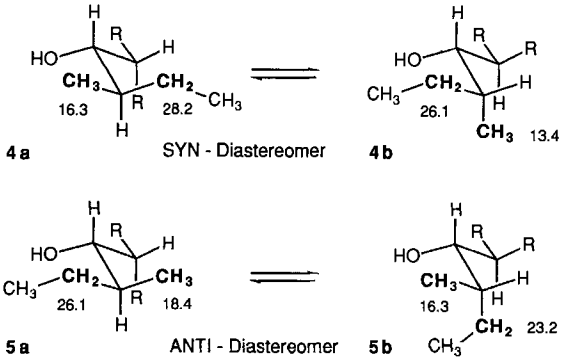
Table 1. ^{13}C-NMR chemical shifts of diastereomeric compounds of established relative configuration

		Stereochemically Caused Difference in Chemical Shift (ppm)	Reference
		- 3.0 + 3.1	9)
		- 2.9 + 3.0	9)
		- 2.0 + 2.2	10)
		- 3.0 + 3.1	10)
		- 2.4 + 2.5	11)
		- 3.2 + 3.5	11)
		- 3.7 + 3.7	8)
		- 3.9 + 3.8	12)
		- 3.3 + 2.5	12)

* Assignment questionable

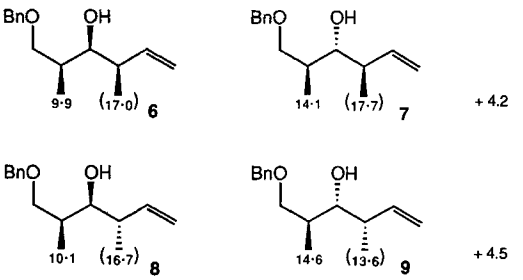
isomer to 24.65 and 17.35, respectively, reproducing the stereochemically caused chemical shift differences reported in Table 1. These differences depend on the population of the **a** and **b** conformations: If **4a** and **5a** are the predominant conformers, the differences in chemical shifts between the diastereomers should be approximately 2 ppm. If **4b** and **5b** are the predominant conformers, the differences should be approximately 3 ppm. If an **a** conformer in the one series and a **b** conformer in the other series are predominant, one carbon signal should show the same chemical shifts in both diastereomers, whereas the other carbon signal should show

Scheme 2



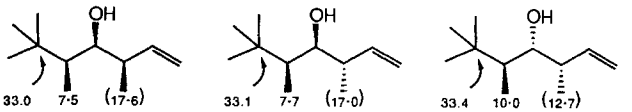
differences of up to 5 ppm. Such a situation seems to hold for the alcohols **6**–**9**. The *syn* isomers **6** and **8** should populate a conformation corresponding to **4b**, allowing an internal hydrogen bond between the hydroxy and the ether group. The *anti* diastereomers **7** and **9** should in turn prefer a conformation corresponding to **5a**, in order to establish internal hydrogen bonds. This should maximize the chemical shift differences in the methyl signal, as can be taken from the published ^{13}C-NMR data[9] (the signals of the carbons carrying the benzyloxy group could not be assigned with confidence and should not show significant chemical shift differences). This situation thus becomes equivalent to that found in β-hydroxy carbonyl compounds[5].

Scheme 3



Another series, in which differences in chemical shifts between the stereoisomers were confined to the methyl signal, is given by the compounds **10**, **11**, and **12** of tentative relative configuration.

Scheme 4

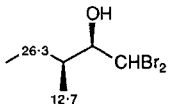
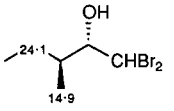
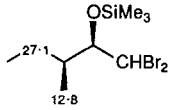
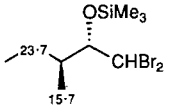
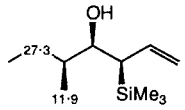
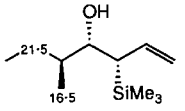
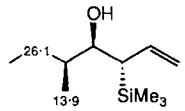
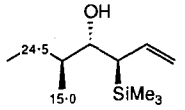
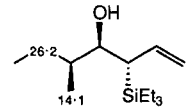
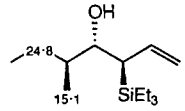
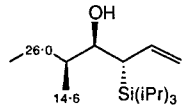
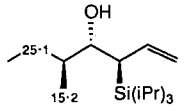
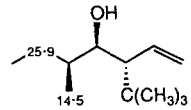
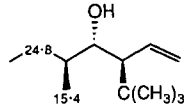


While the signals of the methyl groups showed the expected chemical shift differences, those of the tertiary carbons did not. In view of the bulk of the *tert*-butyl group it is likely that the conformers **4b** and **5a** are the predominant

ones, in which the *tert*-butyl group is sterically least encumbered. The observed effects thus support the provisional structural assignments.

The diagnostic differences in the ^{13}C-NMR chemical shifts reported in Table 1 can also be seen with other pairs of diastereomers, cf. Table 2. The structures shown have been tentatively assigned, based on the observed differences in the ^{13}C-NMR chemical shifts. It may be noted that the size of the diagnostic differences may be normal (entries 1 and 2), increased (entry 3) or progressively smaller as the silyl substituent increases in size (entries 4–7). These changes in the magnitude of the chemical shift differences are not reproduced by the simple considerations given above.

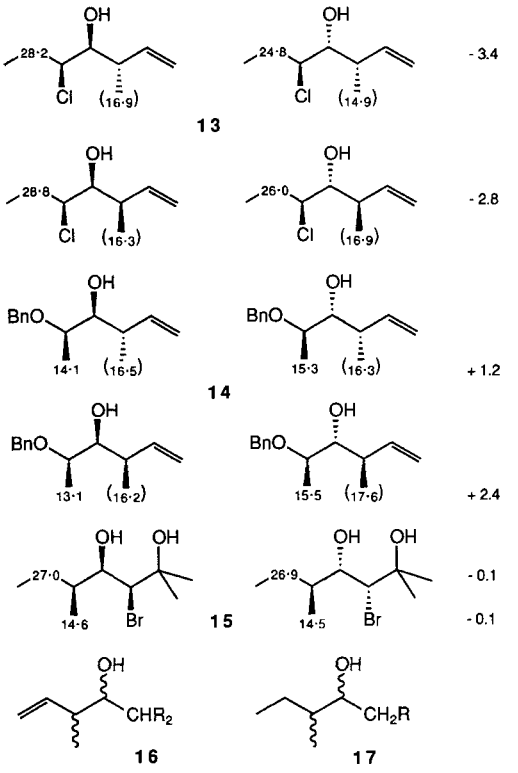
Table 2. ^{13}C-NMR chemical shifts of diastereomeric compounds of tentative relative configuration

			Stereochemically Caused Difference in Chemical Shift (ppm)	Reference
1)			- 2.2 + 2.2	14)
2)			- 3.4 + 2.9	14)
3)			- 5.8 + 4.6	15)
4)			- 1.6 + 1.1	15)
5)			- 1.4 + 1.0	15)
6)			- 0.9 + 0.6	15)
7)			- 1.1 + 0.9	15)

Extensions and Limitations

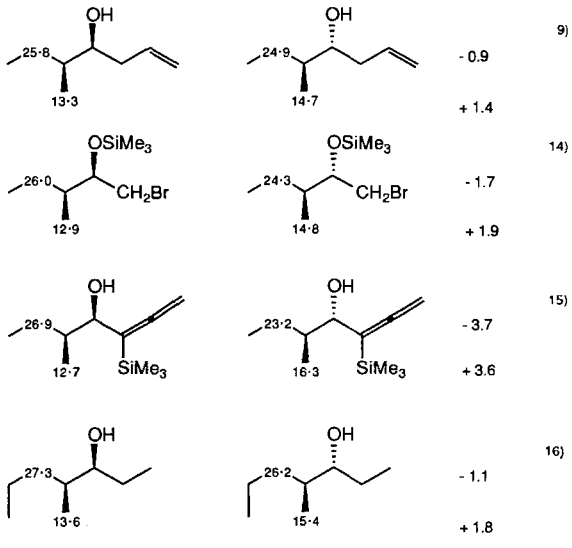
It is of interest to learn whether these rules still hold in cases in which a heteroatom is substituted for either the methyl or the methylene group of the *sec*-butyl structure in **3**. The data in Scheme 5 show that the trends can still be recognized when such a heteroatom is a chlorine, cf. the isomers of **13**[15], or an oxygen atom, cf. the isomers of **14**[9]. However, the effects are becoming too small to be of diagnostic value.

Scheme 5



It is not surprising that the situation becomes unpredictable in cases in which the conformer population and the kind of available conformers is determined by intramolecular hydrogen bonding. This is demonstrated by the negligible chemical shift differences at the carbons of interest between the isomers of **15**[14]. For another example of this sort see ref.[5].

Scheme 6



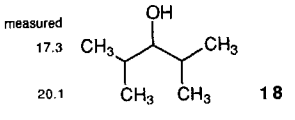
The considerations[8] detailed above should allow a similar analysis for the partial structures **16**. However, the data available, cf. the values in brackets in Table 1 and in Scheme 5, show that neither the chemical shift of the methyl group (nor that of vinylic carbon) displays reliable structure-specific differences for the *syn* and *anti* isomers.

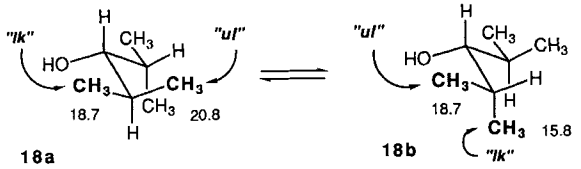
On the other hand, the simple consideration of preferred conformations would not predict that the above-mentioned effects should be seen with compounds of the type **17**, the less substituted analogs of **3**. Yet, in the few cases for which data are available (cf. Scheme 6) similar albeit somewhat smaller differences in the chemical shifts of the diastereomers have been recorded.

Assignment of Chemical Shifts for Diastereotopic Methyl Groups

The methyl groups in the diisopropylcarbinol **18** are diastereotopic. The fact that such methyl groups show different chemical shifts[17] is nowadays covered in introductory texts on NMR spectroscopy[18]. In a classical paper, Roberts[19] pointed out that conformational equilibria may have a profound effect on the chemical shift differences between diastereotopic groups. Roberts found that in a series of isopropylcarbinols one methyl signal had a practically constant chemical shift, around $\delta = 17.3$, whereas that of the other methyl group varied. Assuming that a single conformation, corresponding to **18b** would be the preferred one, he suggested that the $\delta = 17.3$ signal represents the *ul* methyl group in **18**[20], the one which is in this particular conformation farthest remote from the residues on the other side of the carbinol. As it will be shown here, Roberts' suggestion is probably incorrect.

Scheme 7

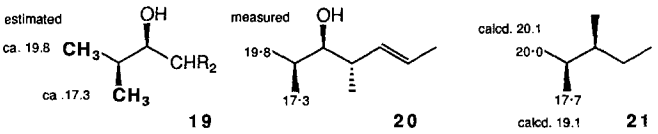




Based on the discussion in the earlier paper[8] we note that the alcohol **18** should exist mainly in the two conformations **18a** and **18b**, which are enantiomorphic and hence isoenergetic and equally populated. For these conformers the chemical shifts of the diastereotopic methyl groups can be predicted[8] (based on $\delta = 24.6$ for isobutane CH_3) as indicated in Scheme 8. These shifts average to $\delta = 19.8$ for the *ul* methyl group and to $\delta = 17.3$ for the *lk* methyl group, in reasonable agreement with the experimental values.

These predicted values for the chemical shifts of diastereotopic methyl groups should apply to all compounds of type **19**. The agreement with experimental values is good, as may be seen for the isopropylcarbinol **20**[21] and many similar compounds reported in ref.[10,11,21].

Scheme 8



Chemical shifts for diastereotopic methyl groups had been assigned previously for the hydrocarbon **21**[6,22] and for related steroidal side chains[23]. Here a weighted average of conformer populations had to be taken into account. This makes it clear that the situation with compounds of type **19** is fortunate, because only two local conformations need to be considered for the assignment of the chemical shifts of the diastereotopic methyl groups.

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CAS Registry Numbers

6: 124377-68-0 / 7: 73814-78-5 / **8**: 83024-75-3 / **9**: 95273-31-7 / **10**: 124318-03-2 / **11**: 124377-69-1 / **12**: 124377-70-4 / **13** (isomer 1): 124377-71-5 / **13** (isomer 2): 124377-72-6 / **13** (isomer 3): 124377-73-7 / **13** (isomer 4): 124377-74-8 / **14** (isomer 1): 124377-75-9 / **14** (isomer 2): 124377-76-0 / **14** (isomer 3): 124377-77-1 / **14** (isomer 4): 124377-78-2 / **15** (isomer 1): 124318-04-3 / **15** (isomer 2): 124377-79-3 / **18**: 600-36-2 / **20**: 123619-73-8 / **21**: 565-59-3

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[311/89]