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NORMALIZED YTTERBIUM INDUCED ^{13}C-NMR SHIFTS AS A SIMPLE AID FOR STRUCTURAL AND ^{13}C SIGNAL ASSIGNMENTS IN MULTIFUNCTIONAL AND NATURAL COMPOUNDS[1]

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Abstract—The LIS-RS analysis described in the preceding communication was applied to phenols, ethers, esters, chromanes, and nitrogen derivatives. For most functionalities the Cβ–RS values are in the range of 40–50%; the smaller Cγ and Cδ values vary consistently as a function of the stereochemistry. Only the induced shifts in acetoxy compounds show no significant conformational dependence. The binding strength at different complexation sites in one molecule differs often enough for a simple analysis, as in monofunctional systems. In other cases the RS variations even in multi binding site compounds such as quinine still allow ^{13}C-NMR signal reassignments.

Lanthanide induced shifts (LIS) provide an extremely convenient help for both structural and ^{13}C-NMR line assignments for all molecules which can selectively bind a lanthanide ion. The compound quantities needed for the measurement are only limited by the spectroscopic requirements, and the samples can be easily isolated after the measurement by extracting the lanthanide in slightly acidic water from the usual substrate solution in lipophilic solvents. Another advantage over functionalization and subsequent ^{13}C-NMR analysis is, that even in complex structures the induced shifts can be easily followed by incremental addition of the shift reagent (LSR). In the preceding communication[2] we have shown for a large series of alcohols and ketones, that normalized Yb(fod)$_3$ induced ^{13}C-NMR shifts (RS-values) allow a simple evaluation of the geometric situation of carbon atoms which are in the vicinity of the Cα atom closest to the binding site. The experimentally found, and theoretically predicted RS values usually lead to a clear distinction of the different atoms. In most cases it will be sufficient to determine the induced shifts, relative to Cα (RS ≡ 100%), after 1–2 additions of the shift reagent (e.g. 5 mole-% to 1 mol substrate), which needs not even to be weighted. In this communication we want to explore the use of the method for other functionalities, particularly to those occurring in natural products, and to study the behaviour of molecules which exhibit several competing binding sites.

The usually found sequence[3] in binding capacity to lanthanide reagents (LSR) is cyclic amines > acyclic amines > alcohols > ketones > cyclic ethers > acyclic ethers > carboxylic esters > ketals. This sequence can change to some degree, mainly due to steric hindrance around the binding site, and very much due to the presence of neighbouring binding atoms (see below). If the functionalities in a structure are sufficiently far apart from each other, which is frequently the case in natural products, polyfunctional compounds will in the presence of small LSR quantities often bind essentially at one center, as demonstrated below. In addition, functionalization of OH or NH groups can be used to block some undesirable binding sites; selective acetylation or methylation often will be sufficient, but silylation with bulky groups might be preferable.[4]

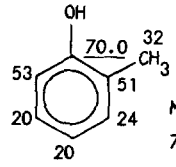
Although the present investigation of multifunctional compounds is less exhaustive than the preceding analysis with alcohols and ketones,[2] representative examples (Scheme 1) and tabulated data[5] demonstrate, that normalized induced shift values RS, relative to Cα ≙ 100%, again can be used in a simple way for structural and ^{13}C NMR line assignments. If Yb is applied for the shift reagent, contact contributions are minimized, but more visible in aromatic as compared to aliphatic skeletons.[3,6]

Oxygen containing binding sites (*phenols, ethers, carboxylic esters phenols*) show puzzling behaviour with Eu or Pr shift reagents, but with Yb typical RS values are observed for Cβ (50–55%) and for Cγ (anti 20–25%, gauche 30–35%); the p- (δ-) carbon shows, however, larger shifts (RS ~ 20%) due to mesomeric effects (see **1**, Table A)[5,6–9].

Methoxy groups are weak binding sites (Table B)[5,6] but the relative shifts illustrated with **2–4** clearly allow to differentiate between the atoms Cβ–Cζ and their orientation with respect to the functional group.[10] *Cyclic ethers*, such as tetrahydropyran,[5] or *epoxides*[11] (see **5,6**) provide stronger complexing sites and are characterized by similar RS at both Cα atoms (≡ 100%), by 40–45% RS at Cβ and RS = 16–39% at Cγ, strongly dependent on the conformation.[11]

Vicinal oxygen groups, such as in 1,2-dimethoxybenzene[5] or in podophyllotoxin[12] **7** can bind the lanthanide strongly by bifunctional complexation, so that even a hydroxy group leads to smaller, but competitive binding (*cf* C7 in **7**). *Ketals*, on the other hand, are the weakest complexing sites as compared to the other oxygen derivatives, which is demonstrated both in **7** and in the spirostanes diosgeninacetate (Table E)[5] or hecogeninacetate **8** (Scheme 1).

In *carboxylic esters* (Table E,[5] **8, 9**) the largest shift



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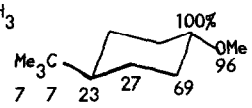

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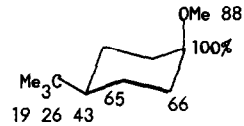

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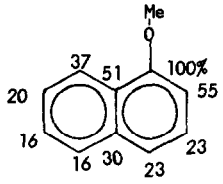

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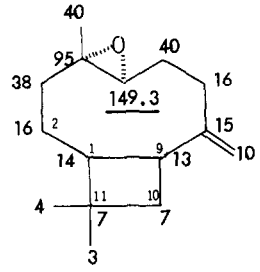

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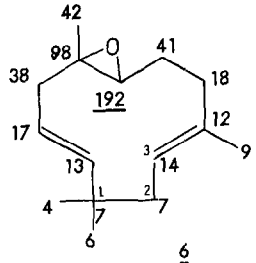
(Caryophyllenepoxide)



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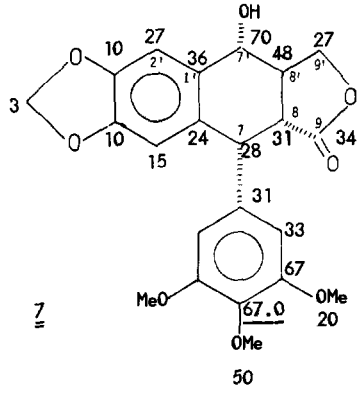

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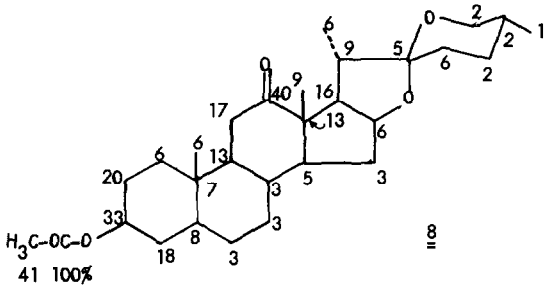
(Podophyllotoxin)



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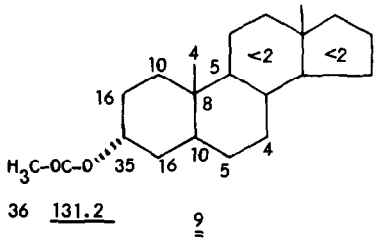
(Hecogenin-OAc ; similar RS observed in 3β-OAc-5αH-androstane[5])



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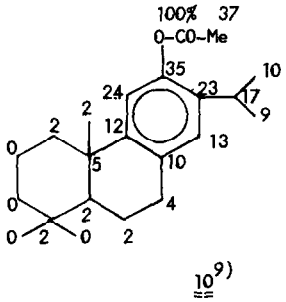
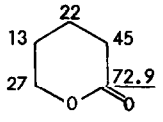


10[9]

(3 -α-OAc-5αH- Androstane)



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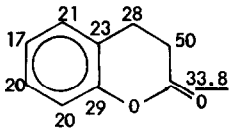

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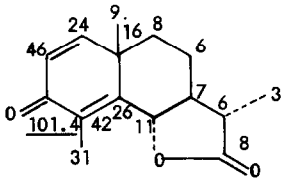

(α- Santonin)

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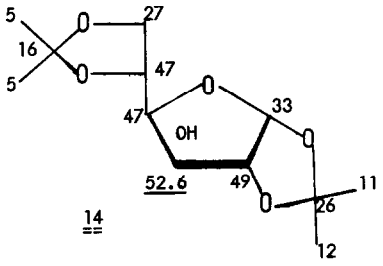

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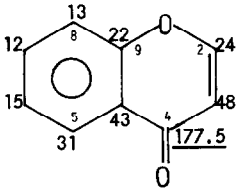

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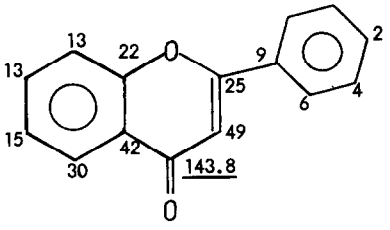

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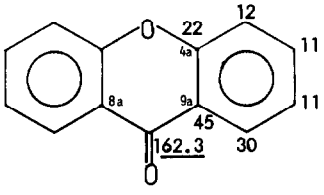

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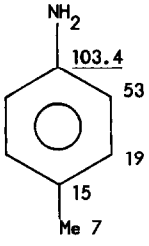

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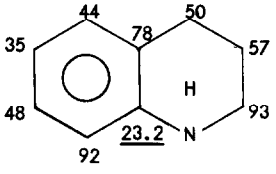

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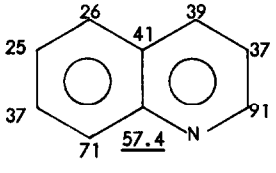

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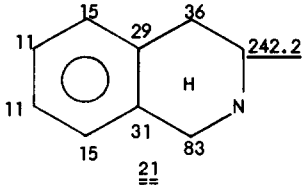

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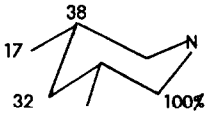

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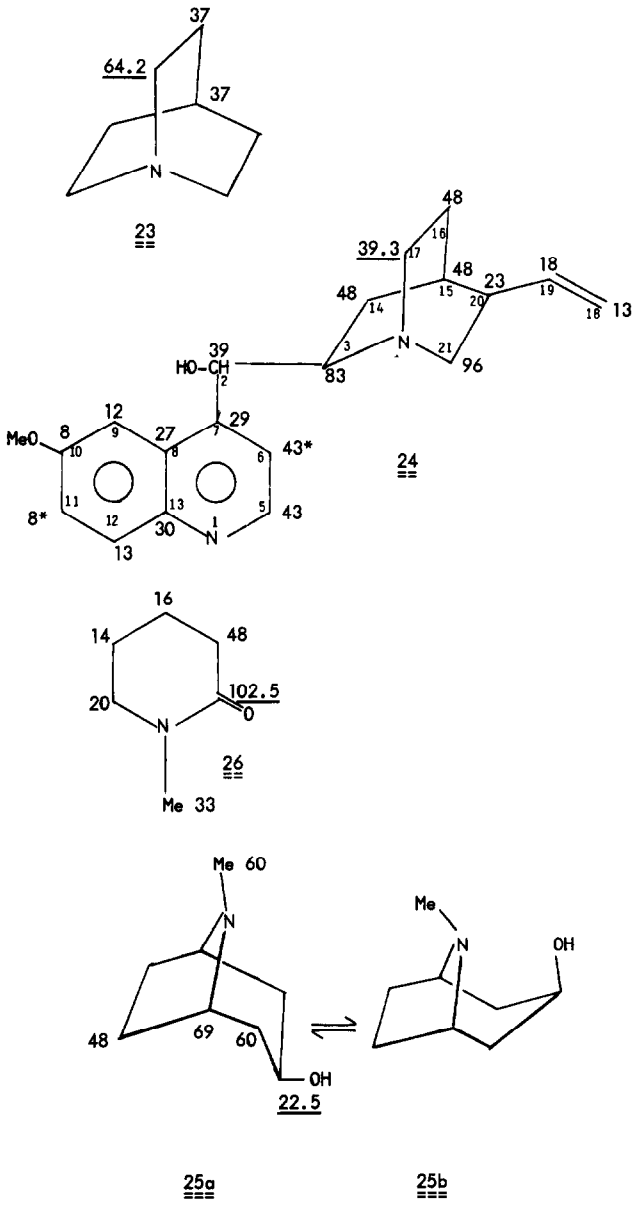

Scheme 1. Yb(fod)$_3$-induced ^{13}C-NMR-shifts (C_α in [ppm, *S*], or [%, RS]; other C in [%, RS].

is always induced at the carbonyl ($\equiv 100\%$ RS); the β carbon shows RS = $40 \pm 4\%$ in acetates and RS = $45 \pm 5\%$ in fatty acid methyl esters; for the γ carbon one observes $34 \pm 2\%$ at C–OAc, but by 5–10% smaller values for OCH_3 in fatty acid esters; the other RS values in acetates decrease as follows: Cδ 15 ± 1, Cϵ 8 ± 3, Cζ 5 ± 3, Cξ 3 ± 2. Whereas topological assignments on the basis of RS values are straightforward, the esters seem to be the only class of compounds where a stereochemical analysis is difficult due to small RS differences between epimers (of **8,9** etc[5]). Due to the carbonyl oxygen binding site, which is more remote from the skeleton than the alkyl oxygen, the RS values differ only by $< 2\%$ between e or a substituted steroidal acetates (Table E)[5]. A particular difficulty leading to additional RS variations arises with esters bearing conformationally unbiased alkyl groups, such as isopropyl substituent in vicinal position to acetoxy. Thus, in ferruginol[9] **1(** (Table E)[5] RS variations, e.g. for Cδ are observec from 17 to 24% and for Cϵ from 8 to 17%, which car be the consequence of a change of an isopropy rotamer population upon complexation with th LSR.

The *lactones* (**11, 12**) again show 45–50% at Cβ anc 22–29% RS at Cγ, with the higher values at Cγ–O α-Santonin[13] (**13**), bearing a lacton and an oxo func tion, is another example for the accessibility of RS values in bifunctional compounds with large differences in binding capacity. Derivatives with a large number of similar functionalities represent th limit of the method, as illustrated with the *furanos* diacetonide **14**. Ketalization makes the sugar solubl enough in chloroform for LIS measurements anc helps to suppress binding to the former hydroxy groups, but even small amounts of Yb(fod)$_3$ seem t

bind simultaneously to too many sites. Measurements of the free carbohydrates in aqueous solution with water soluble shift reagents[3] are here an attractive alternative.

In *chromones* (**15**) the lanthanide binds as expected to the carbonyl oxygen; this was concluded earlier from ^{1}H-LIS studies[14] with flavones (**16**) and is obvious from the ^{13}C shifts induced by Yb(fod)$_3$ (see Table C)[5]. The Cβ–RS values are consistently $44 \pm 4\%$, and the Cγ–RS values show the characteristic difference between anti (C2,9: $23 \pm 2\%$) and syn orientation (C5: $31 \pm 1\%$). Similar relative shifts are found in the 2,3-dihydroderivatives of **15** and **16** and in xanthone (**17**). The observed RS support published assignments[15] and allow the distinction of C5 and C6 in chromone **15**, which due to a shielding difference of only 0.5 ppm[15] was not possible before.

Amines are particularly sensitive to contact contributions and therefore show frequently confusing ^{13}C-LIS with Eu, Pr and many other LSR[3,16–25] (Tables F, G)[5]. Yb reagents, characterized by the smallest contact shifts,[3,17,22–25] give a more consistent pattern of normalized RS values (Table 1), although the variations are larger than observed with oxygen derivatives, and a smaller number of compounds (*cf* Scheme 1; Tables F, G)[5,16–25] was investigated in the present work. It should be noted that the relative shifts are usually larger on aromatic as compared to aliphatic carbon atoms (see, e.g. **19**). The binding constants to nitrogen are high, but obviously very dependent on the environment. Thus, the LIS (S in [ppm], for the 1:1 complex) are, e.g. for **23** 64, for tributylamine 10, for dibutylamine 51, for n-butylamine 142[5]. This observation, and a similar difference between, e.g. tetrahydropyran and dipropyl ether, suggest a strong entropy effect on the binding constants. In multifunctional compounds, as in many alkaloids, the lanthanide will preferentially complex at the nitrogen, but secondary binding sites such as hydroxy groups can lead to shifts, which partially are difficult to analyze (see **24**). Nevertheless, many RS differences allow unambiguous assignments, as in quinine (**24**) where the original assignments[26] for C6 and C11 had to be reversed. Conformational change upon complexation such as a chair-boat interconversion in pseudotropine[27] (**25a**, **26b**) can also obscure the normal RS values. The Yb(fod)$_3$ binding in *amides* or *lactams* (**26**) occurs at the carbonyl oxygen and to a lesser degree at the nitrogen, which is visible in the corresponding RS value.[5]

EXPERIMENTAL

LIS-NMR data were obtained as described before;[2] for some compounds the RS values were determined by comparing the induced shifts at Cα with other carbon signals after few additions of shift reagent. The line broadening observed after adding up to 10 mol-% LSR usually was negligible, except for the aliphatic carbon signals in quinine (**24**).

The compounds were commercially available, or taken from earlier studies;[8,27] their purity was usually not checked, except by ^{13}C-NMR , since no effort was made to obtain intrinsic (or bound) shifts for the complexes.

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Table 1. Yb(fod)$_3$-Induced shifts in some nitrogen compounds[a]

	Cβ	Cγ anti	Cγ syn	Cδ
Prim. Amines, aliphatic	44–52	17–24	38	21
Prim. Amines, aromatic	46–56	16–26	41	13–23[b]
Sec. Amines, aliphatic	35–48	17–23	25–33	10–26
Tert. Amines, aliphatic	37–68	36		< 5

a) RS values [%] relative to Cα≡100%; b) the larger RS are observed at aromatic Cδ.

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