Toward Creation of a Universal NMR Database for Stereochemical Assignment: The Case of 1,3,5-Trisubstituted Acyclic Systems

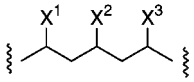
by **Yoshihisa Kobayashi**, **Choon-Hong Tan**, and **Yoshito Kishi***

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, USA

Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

Using the diastereoisomeric triols **1a**–**d** (*Fig. 1*) and examples summarized in *Fig. 2*, the central C-atom of acyclic 1,3,5-triols is demonstrated to exhibit a distinctive chemical shift that is *dependent* on the 1,3- and 3,5-relative configuration, but is *independent* of the functionalities present outside of this structural motif. These NMR characteristics are then used to predict the relative configuration of several natural products (*Fig. 7*). In addition, an example is given to show the possibility of assembling an NMR database for a larger array of functional groups from NMR databases of smaller arrays of functional groups.

Through our work on palytoxin [1], AAL toxins/fumonisins [2], maitotoxin [3], and universal NMR databases [4], we have experimentally demonstrated that steric and/or stereoelectronic interactions between the structural motifs connected either directly or with a one-CH_2 bridge are significant, whereas interactions between the structural motifs connected with a two- or more-CH_2 bridge are almost negligible. On this basis, we have noticed that 1,3,5-trisubstituted acyclic compounds, represented by **A**, may exhibit a unique characteristic: the central C-atom may exhibit a distinctive chemical shift which is *dependent* on the X^1/X^2- and X^2/X^3-relative configuration, but is *independent* of the functionalities present outside of this structural motif[1]). One might be concerned that, through the substituents X^1 and X^3, functional groups present outside of the 1,3,5-trisubstituted moiety might indirectly affect the chemical shifts of these nuclei. However, upon a close examination of the cases previously studied in our laboratories, we speculate that such indirect steric and/or stereoelectronic effects on the chemical shifts in question is negligibly small [2–4].



A

To test this hypothesis, we have chosen a 1,3,5-triol system ($X^1 = X^2 = X^3 = OH$ in **A**) as an example, synthesized the four possible diastereoisomers

[1]) This analysis may be applicable for the chemical shift of the H-atom attached to the central C-atom.

1a–**d**, and measured the ^{13}C chemical shifts in (D_6)DMSO and (D_4)methanol (*Fig. 1*)[2])[3]).

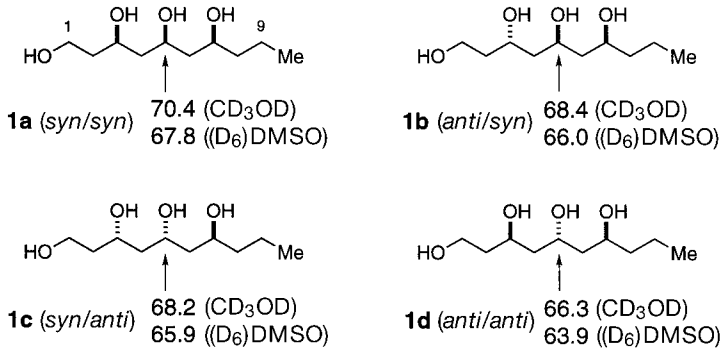


Fig. 1. *^{13}C-NMR Chemical shifts* (ppm; in (D_6)DMSO and CD_3OD) *of C(5) of* **1a**–**d**

A large number of natural products and synthetic compounds containing the partial structure of $-CH(OH)CH_2CH(OH)CH_2CH(OH)-$ in an acyclic system are recorded in the literature. However, few of these are stereochemically well-defined, with the assigned chemical shifts being reported in (D_6)DMSO or CD_3OD[3]). *Fig. 2* summarizes the distribution of the chemical shifts for the central C-atom of each stereochemical

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[2]) The triols **1a**–**d** were synthesized in 13 steps, *i.e.*, 1. $Me(CH_2)_2CHO + CH_2{=}CHCH_2MgBr$, THF, 0°, 2. MPM-Cl, NaH, Bu_4NI, DMF, 3. OsO_4, *N*-methylmorpholine *N*-oxide (NMO), THF/H_2O, followed by $Pb(OAc)_4$, benzene, 4. $CH_2{=}CHCH_2MgBr$, THF, 0°, 5. Ac_2O, Py, 4-(dimethylamino)pyridine (DMAP), 6. 2,2-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O, followed by chromatographic separation. 7. KOH, MeOH, 8. BnBr, NaH, Bu_4NI, DMF, 9. OsO_4, NMO, THF/H_2O, followed by $Pb(OAc)_4$, benzene, 10. $CH_2{=}CHCH_2MgBr$, THF, 0°, 11. OsO_4, NMO, THF/H_2O, followed by $Pb(OAc)_4$, benzene, 12. $NaBH_4$, MeOH, 13. H_2, Pd–C, MeOH, followed by chromatographic separation. The relative configuration of the products obtained at the step 4 was established from the ^{13}C-NMR spectra of the acetonide of 1,3-diols, whereas that at the step 10 was deduced from the ^{13}C-NMR spectra of their hydrogenation/hydrogenolysis products, *cf.* the symmetry/asymmetry present in **IIIa**–**c**. ^{13}C-NMR (CD_3OD, 100 MHz): **1a**: 60.0 (C(1)); 40.9 (C(2)); 68.8 (C(3)); 45.4 (C(4)); 70.4 (C(5)); 45.1 (C(6)); 71.0 (C(7)); 41.0 (C(8)); 19.7 (C(9)); 14.5 (C(10)); **1b**: 60.2 (C(1)); 41.5 (C(2)); 66.7 (C(3)); 45.9 (C(4)); 68.4 (C(5)); 45.7 (C(6)); 71.1 (C(7)); 40.9 (C(8)); 19.7 (C(9)); 14.5 (C(10)); **1c**: 60.0 (C(1)); 40.9 (C(2)); 68.8 (C(3)); 46.1 (C(4)); 68.2 (C(5)); 45.7 (C(6)); 68.7 (C(7)); 41.5 (C(8)); 19.9 (C(9)); 14.5 (C(10)); **1d**: 60.2 (C(1)); 41.4 (C(2)); 66.9 (C(3)); 46.5 (C(4)); 66.3 (C(5)); 46.2 (C(6)); 68.9 (C(7)); 41.4 (C(8)); 19.9 (C(9)); 14.5 (C(10)). ^{13}C-NMR ((D_6)DMSO, 100 MHz): **1a**: 58.0 (C(1)); 40.4 (C(2)); 66.2 (C(3)); 44.8 (C(4)); 67.8 (C(5)); 44.5 (C(6)); 68.2 (C(7)); 39.6 (C(8)); 18.3 (C(9)); 14.2 (C(10)); **1b**: 58.1 (C(1)); 41.0 (C(2)); 64.2 (C(3)); 45.4 (C(4)); 66.0 (C(5)); 45.1 (C(6)); 68.4 (C(7)); 39.6 (C(8)); 18.3 (C(9)); 14.2 (C(10)); **1c**: 58.0 (C(1)); 40.4 (C(2)); 66.5 (C(3)); 45.3 (C(4)); 65.9 (C(5)); 45.1 (C(6)); 66.1 (C(7)); 40.2 (C(8)); 18.5 (C(9)); 14.2 (C(10)); **1d**: 58.2 (C(1)); 41.0 (C(2)); 64.5 (C(3)); 45.8 (C(4)); 63.9 (C(5)); 45.6 (C(6)); 66.3 (C(7)); 40.2 (C(8)); 18.5 (C(9)); 14.2 (C(10)).

[3]) The solvent-effect studies on the two contiguous propionate NMR databases indicated no significant intramolecular interactions present in (D_6)DMSO (the residual solvent signal was set at 39.5 ppm) and CD_3OD (the residual solvent signal was set at 49.0 ppm) but suggested formation of intramolecular H-bonding networks in $CDCl_3$ [4a].

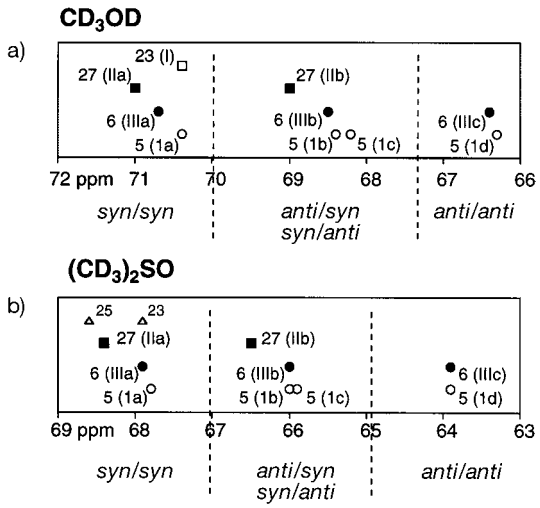

Fig. 2. *Chemical-shift distribution of the central C-atom of acyclic 1,3,5-triol systems.* The panels *a* and *b* show the distribution of chemical shifts in CD_3OD and $(D_6)DMSO$, respectively. △ represents the data taken from aflastatin A, with indication of the C-atom number. Likewise, □ from the degradation product **I** of aflastatin A, ■ from **IIa**,**b**, ● from **IIIa**–**c**, ○ from **1a**–**d**.

array in question[4]). Three sub-groups are easily recognized in both solvents, with all the *anti*/*anti* cases clustering in the range of 66.3 ± 0.5 ppm (CD_3OD) and 63.9 ± 0.5 ppm ($(D_6)DMSO$), all the *anti*/*syn* and *syn*/*anti* in the range of 68.6 ± 0.5 ppm (CD_3OD) and 66.2 ± 0.5 ppm ($(D_6)DMSO$), and all the *syn*/*syn* in the range of 70.7 ± 0.5 ppm (CD_3OD) and 68.2 ± 0.5 ppm ($(D_6)DMSO$). This exercise demonstrates that the chemical shift of the central C-atom depends primarily on the C(1)/C(3)- and C(3)/C(5)-relative configuration but is independent of the rest of the functionalities present in the molecule.

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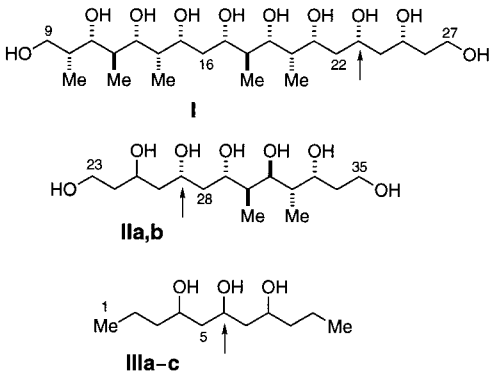
[4]) A *SciFinder* sub-structure search (July, 2000) gave 420 hits containing this partial structure. Among them, aflastatin A and one of its degradation products, **I**, met with these conditions [5]. However, related to the work of universal NMR databases, we have synthesized and characterized **IIa**,**b** and **IIIa**–**c**, which did add valuable data points to construct this graph.



We have noted the possibility that an NMR database for a larger array of functional groups could be assembled from NMR databases of smaller arrays of functional groups [4b]. In connection with this objective, the NMR database of a 1,3-diol such as **2a**,**b**[5]) is intriguing (*Fig. 3*)[6]). The ^{13}C chemical shift indicated for the *syn*-diol **2a** is downfield by *ca.* 2 ppm than that for the *anti*-diol **2b** (for a related observation, see [6]). Interestingly, this phenomenon occurs in each *syn*/*anti* 1,3-diol pair studied, including every *syn*/*anti* pair of each 1,3-diol system present in the structures shown in *Figs. 1* and *4*. Upon comparison of the two databases summarized in *Figs. 1* and *3*, one can recognize a series of additivity increments to predict the chemical shift for the central carbon of 1,3,5-triols based on the 1,3-diol database; the chemical shift is found *ca.* 4 ppm downfield for **1a** (*syn* + *syn* = 2 + 2), and *ca.* 2 ppm downfield for **1b** (*anti* + *syn* = 0 + 2) and **1c** (*syn* + *anti* = 2 + 0), in reference to the corresponding chemical shift for **1d** (*anti*/*anti*)[7]).

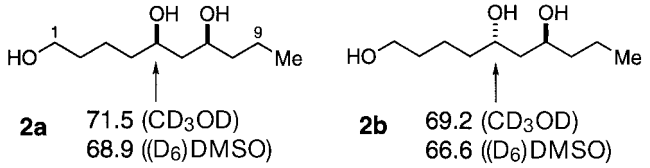


Fig. 3. *^{13}C-NMR Chemical shifts* (ppm; in (D_6)DMSO and CD_3OD) *of C(5) of 1,3-Diols* **2a** *and* **2b**

During the course of this study, we recognized an interesting trend with regard to the chemical shift of the C-atom indicated by an arrow in **3a**,**b**; the effect of a primary alcohol on the chemical shift is approximately equal in magnitude (*ca.* 2 ppm) to that of an *anti* secondary alcohol (*Fig. 4*) (*cf.* C(5) of **1b** and **1d** *vs.* C(3) of **3a** and **3b**). This trend is observed consistently in **1a**–**d**, as well as in the examples known in the literature[8]). Similarly, we have examined an effect of an olefinic bond on the ^{13}C chemical shift of the 1,3-diol system. Among the three olefin-

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5) The diols **2a**,**b** were synthesized in a similar route to the one given for the synthesis of **1a**–**d**. ^{13}C-NMR (CD_3OD, 100 MHz): **2a**: 62.9 (C(1)); 33.7 (C(2)); 22.9 (C(3)); 38.4 (C(4)); 71.5 (C(5)); 44.9 (C(6)); 71.4 (C(7)); 40.9 (C(8)); 19.7 (C(9)); 14.5 (C(10)); **2b**: 62.9 (C(1)); 33.7 (C(2)); 23.1 (C(3)); 39.0 (C(4)); 69.2 (C(5)); 45.6 (C(6)); 69.0 (C(7)); 41.5 (C(8)); 20.0 (C(9)); 14.5 (C(10)). ^{13}C-NMR ((D_6)DMSO, 100 MHz): **2a**: 60.8 (C(1)); 32.7 (C(2)); 21.6 (C(3)); 37.3 (C(4)); 68.9 (C(5)); 44.3 (C(6)); 68.5 (C(7)); 39.3 (C(8)); 18.2 (C(9)); 14.2 (C(10)); **2b**: 60.8 (C(1)); 32.7 (C(2)); 21.9 (C(3)); 37.9 (C(4)); 66.6 (C(5)); 44.9 (C(6)); 66.3 (C(7)); 40.2 (C(8)); 18.5 (C(9)); 14.2 (C(10)).

6) This NMR database, originally created for the stereochemical assignment of the 1,3-diol moiety present in the desertomycin/oasomycin class of natural products, should have a wide application. A *SciFinder* sub-structure search (July, 2000) gave 1,143 hits containing the partial structure of 1,3-diol, *i.e.*, **A** with $X^1 = H$ and $X^2 = X^3 = OH$. For example, based on the chemical shifts reported for the C(10) (69.0 ppm, (D_6)DMSO), C(22) (68.8), C(49) (66.8), and C(53) (66.6) C-atoms of theonezolide A [7i], this NMR database predicts its relative configuration at C(8)/C(10), C(22)/C(24), C(47)/C(49), and C(53)/C(55) to be *syn*, *syn*, *anti*, and *anti*, respectively.

7) To formulate an empirical rule, we clearly need to determine and incorporate a proper coefficient for this additivity.

8) A *SciFinder* sub-structure search (July, 2000) gave 74 hits containing the partial structure of **3a**,**b**. The application of 1,3,5-triol database **3a**,**b** for the degradation product of shurimycin A, described as **3** in [7c], revealed the relative configuration of C(21)/C(23) (*anti*), based on the NMR chemical shift of C(21) (66.3 ppm in CD_3OD; $X^1 = H$).

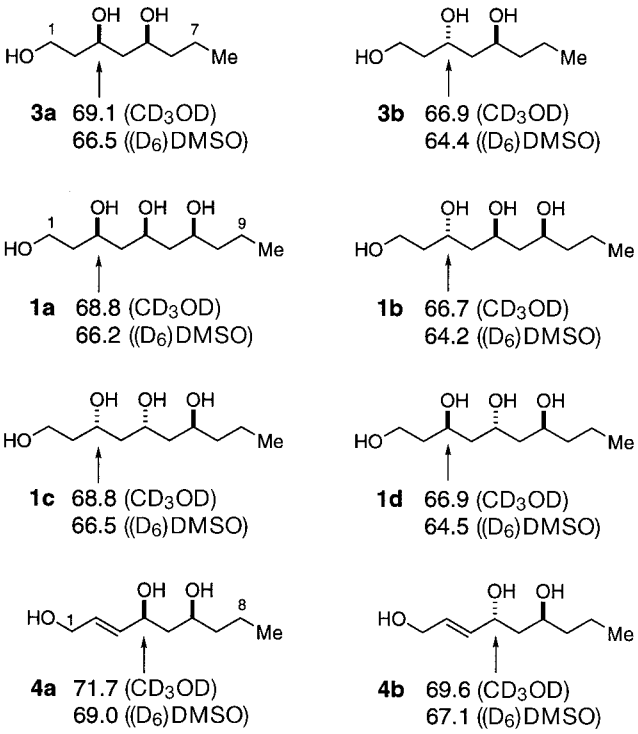

Fig. 4. *^{13}C-NMR Chemical shifts* (ppm; in (D_6)DMSO and CD_3OD) *of C(3) of* **1a–d** *and* **3a**,**b**, *and of C(4) of the olefinic 1,3-diols* **4a** *and* **4b**

substitution patterns often found in polyketide natural products[9]), we have used **4a**,**b**[10]) as an example (*Fig. 4*). The ^{13}C chemical shifts indicated by an arrow again match well with the values reported in the literature[11]).

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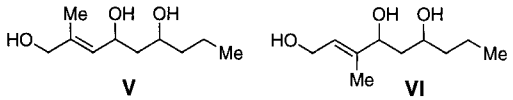
[9]) Two additional olefin-substitution patterns represented by **V** and **VI** are often recognized in polyketide natural products. A *SciFinder* sub-structure search (July, 2000) gave 484, 96, and 17 hits containing an olefin(s) of types **4**, **V** and **VI**, respectively.



V **VI**

[10]) ^{13}C-NMR (CD_3OD, 100 MHz): **4a**: 63.0 (C(1)); 131.1 (C(2)); 134.5 (C(3)); 71.7 (C(4)); 45.3 (C(5)); 70.4 (C(6)); 41.1 (C(7)); 19.7 (C(8)); 14.5 (C(9)); **4b**: 63.1 (C(1)); 129.9 (C(2)); 135.4 (C(3)); 69.6 (C(4)); 45.6 (C(5)); 68.7 (C(6)); 41.3 (C(7)); 19.9 (C(8)); 14.5 (C(9)). ^{13}C-NMR ((D_6)DMSO, 100 MHz): **4a**: 61.0 (C(1)); 129.3 (C(2)); 133.2 (C(3)); 69.0 (C(4)); 44.9 (C(5)); 67.6 (C(6)); 39.7 (C(7)); 18.3 (C(8)); 14.2 (C(9)); **4b**: 61.0 (C(1)); 128.4 (C(2)); 134.2 (C(3)); 67.1 (C(4)); 45.1 (C(5)); 66.0 (C(6)); 40.0 (C(7)); 18.4 (C(8)); 14.1 (C(9)).

[11]) Based on the chemical shifts of C(37) (72.0 ppm in CD_3OD) and C(47) (70.3), the **4a**,**b**-NMR database predicts the C(35)/C(37) and C(45)/C(47) relative configuration of linearmycin A [7b] to be *syn* and *anti*, respectively. Likewise, the C(35)/C(37) relative configuration of oasomycin B [8] is predicted from the chemical shift of C(37) (66.8 ppm in (D_6)DMSO).

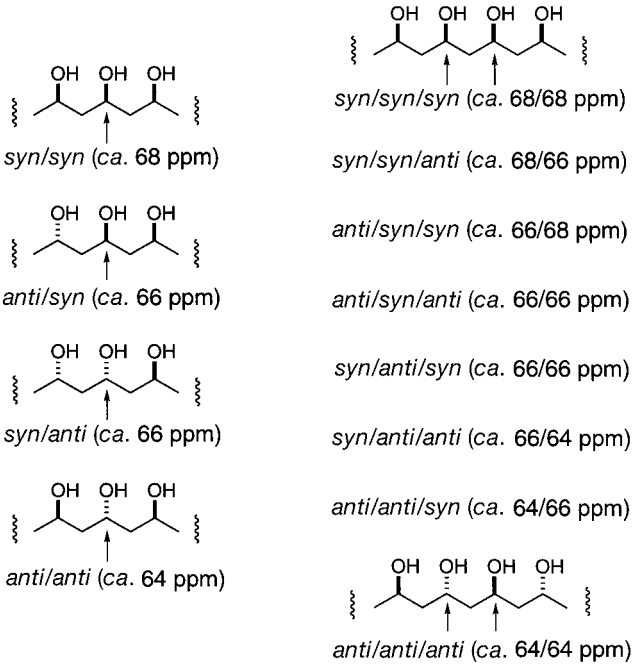


Fig. 5. *^{13}C-NMR Chemical shifts expected for unknown 1,3-polyol systems.* Expected values in (D_6)DMSO for the C-atom indicated by an arrow are shown. Those in CD_3OD are *ca.* 70 ppm (*syn*/*syn*), 68 (*anti*/*syn* and *syn*/*anti*), and 66 (*anti*/*anti*).

It is tempting to apply these patterns to predict the configuration of unknown compounds. *Fig. 5* summarizes a possible outcome for the case of an unknown compound containing a 1,3,5-triol system. Based on the chemical shift of the central C-atom, an *anti*/*anti*, *syn*/*anti* or *anti*/*syn*, or *syn*/*syn* diastereoisomer can be identified. However, this approach alone can not differentiate an *anti*/*syn* diastereoisomer from a *syn*/*anti*[12]). Knowing the chemical shifts of two central C-atoms, it is possible to deduce the relative configuration of 6 out of the 8 possible diastereoisomers for a 1,3,5,7-tetrol system employing this approach (*Fig. 5*)[12]). We should add that this simple approach has successfully been used to assign the relative configuration of the OH groups at C(23), C(25), C(27), and C(29), as well as C(33), C(35), and C(37) of desertomycins/oasomycins (*Fig. 6*) [8]. Similarly, we can suggest the relative configuration of 1,3-polyol systems found in the literature; some of these are summarized in *Fig. 7*.

The universal NMR databases we have created contain configurational as well as conformational information, including the dynamic properties of a given system. Thus far, we have treated the structural portions of the desertomycin/oasomycin class of natural

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[12]) For some cases, discrimination of these (*cf.*, *anti*/*syn vs. syn*/*anti* in the triol series, and *anti*/*syn*/*anti vs. syn*/*anti*/*syn* in the tetrol series) should be possible; for example, the cases where one of the two ends of an unknown compound corresponds to the functional group shown in *Fig. 4*, or to the functional group of $X^1 = H$ (*Fig. 3*).

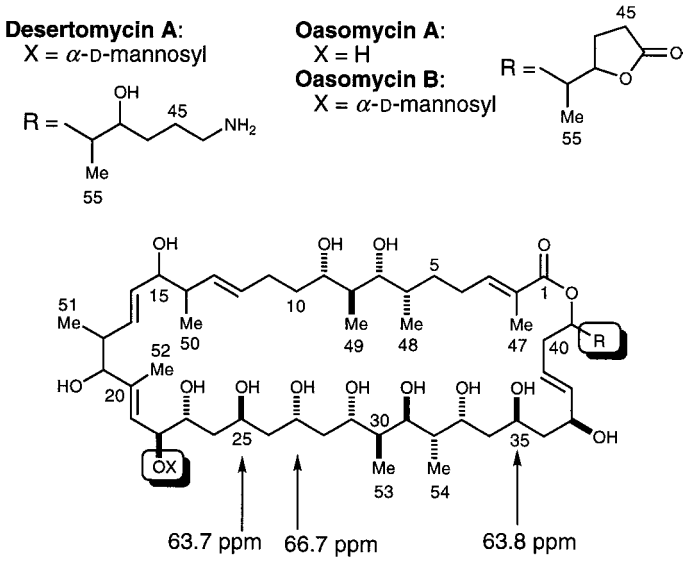

Fig. 6. *^{13}C-NMR Chemical shifts* ((D$_6$)DMSO) *of C(25), C(27), and C(35) of desertomycins/oasomycins*

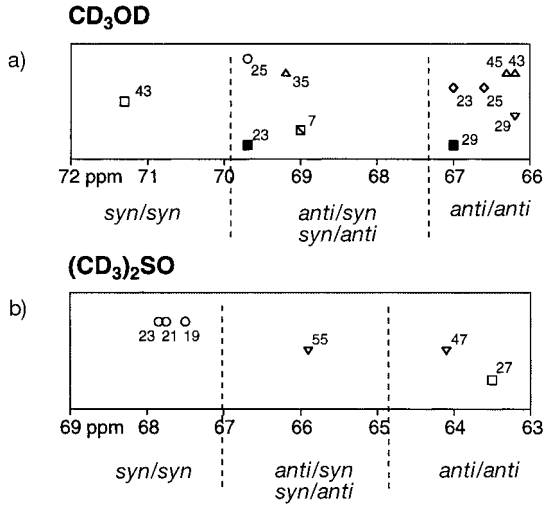

Fig. 7. *Chemical-shift distribution of the central C-atom of 1,3,5-triol systems with unknown configuration*. The panels *a* and *b* show the distribution of chemical shifts in CD_3OD and $(D_6)DMSO$, respectively [7]. *a*) ○ represents the data taken from quinolidomicin A, with indication of the C-atom number. Likewise, △ from linearmycin A, ◇ from shurimycin A, □ from monazomycin, ▽ from malolactomycin A, ⧅ from brasilinolide A, ■ from mathemycin A. *b*) ○ represents the data taken from blasticidin A, with indication of the C-atom number. Likewise, ▽ from theonezoline A, □ from kanchanamycin A.

products as if the macrocyclic lactone rings did not significantly affect their NMR properties. However, we have noticed that the chemical shifts reported for the central C-atoms of the 1,3,5-triols present in desertomycins/oasomycins differ slightly from

those observed for **1a–d** (*Fig. 8*). In this context, the 1,3-diol systems found in the polyene macrolide antibiotics are enlightening. Among a large number of polyene macrolide antibiotics, mycoticin A (known also as flavofungin) [9] is especially intriguing, because complete assignments of the ^{1}H- and ^{13}C-NMR in (D_6)DMSO were accomplished, and also because an X-ray analysis was performed on the structurally closely related roxaticin [10]. The chemical shifts reported for the C(17) (69.28 ppm in (D_6)DMSO), C(19) (67.53), C(21) (62.16), C(23) (62.63), and C(25) (66.28) C-atoms of mycoticin A still follow the general trend, *i.e.*, three sub-groups are recognized with the order of chemical shifts (downfield-to-upfield) being *syn/syn* → *anti/syn* and *syn/anti* → *anti/anti*. However, the absolute values of chemical shifts reported for mycoticin A differ more significantly from those found in **1a–d** than those for desertomycins/oasomycins (*Fig. 8*).

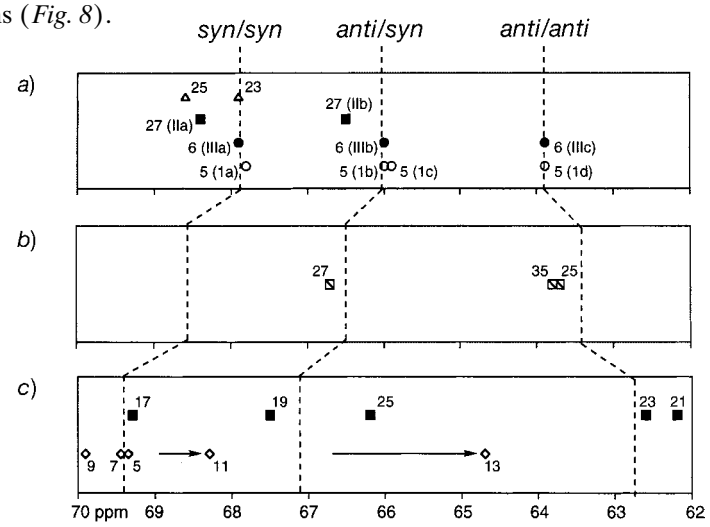

Fig. 8. *Chemical-shift distribution of the central C-atom of 1,3,5-triol systems.* The panels *a*, *b*, and *c* show the distribution of ^{13}C chemical shifts in the acyclic (*Fig. 2*), desertomycins/oasomycins and mycoticin A (■), and filipin III (◇) series in (D_6)DMSO, respectively, with indication of the C-atom number.

In our view, there are at least two reasons for this deviation in the absolute values of chemical shifts. First, it is well-documented that the polyene and 1,3-polyol chains interact with each other transannularly [9b][10], and one can imagine that an anisotropic effect from the polyene chain on the 1,3-polyol chain might have resulted in a deviation on the chemical shifts in question. In this context, the NMR data of filipin III are informative [11]; the chemical shifts for the C(13) (64.7 ppm in (D_6)DMSO) and C(11) (68.3) C-atoms deviate significantly from the expected standard value (*Fig. 8*). Interestingly, the chemical shift of the proton attached to the C(13) is also abnormally shifted upfield[13]). Using the abnormalities of chemical shifts noticed for H–C(13) and C(13) of filipin III as a reference, we speculate the magnitude of anisotropic effects to be relatively small for the case of desertomycins/oasomycins and mycoticin A. Second,

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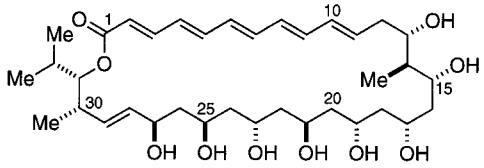
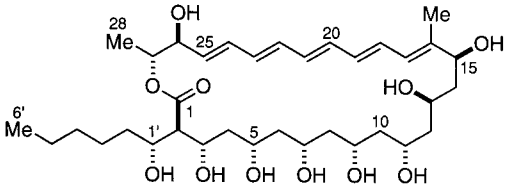
[13]) The chemical shifts of H–C(13) and H–C(11) of filipin III were found to be 3.04 ppm ((D_6)DMSO) and 3.77, respectively [11]. These are significantly upfield-shifted, in reference to the chemical shifts for the proton attached to the central C-atom of **1a** (3.80 ppm, (D_6)DMSO), **1b** (3.81), **1c** (3.80), and **1d** (3.86).



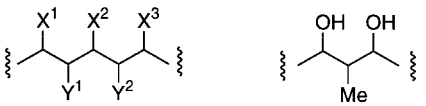
mycoticin A



filipin III

mycoticin A is known to be conformationally relatively rigid, and its preferred conformation is similar to the solid-state conformation of roxaticin, in which the 1,3-polyol chain exists in an extended form [10]. As previously stated, the universal NMR databases contain conformational information, including the distribution of conformer population for a given system. The small observed discrepancy may thus be due to a difference in the population of conformers. This analysis may explain why larger deviations in chemical shifts from the expected values were observed in mycoticin A than in desertomycins/oasomycins. Because of a smaller ring size and also because of the presence of a conjugated polyene, the macrolactone embedding the 1,3,5-triol systems of mycoticin A is conformationally less flexible than that of desertomycins/oasomycins, which is reflected in the ^{13}C chemical shifts.

In summary, it has been recognized, and experimentally proven, that the central C-atom of a 1,3,5-triol system exhibits a distinctive chemical shift which is *dependent* on the 1,3- and 3,5-relative configuration, but is *independent* of the functionalities present outside of this structural motif. A similar phenomenon has been observed for the polyol systems described in *Fig. 4*. We believe that this phenomenon can be extended to more generalized structures such as **B** and the corresponding structures bearing the terminal functionalities shown in *Fig. 4*. We expect that many structural motifs with unique structural characteristics independent of the rest of the functionalities present within a molecule will be identified. In this context, we have recently recognized that the chemical shift of the Me group in the partial structure represented by **C** shows a unique property, and we are currently completing its NMR database.



B **C**

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