A Simple Spectroscopic Method for Assigning Relative and Absolute Configuration in Acyclic 1,2,3-Triols†

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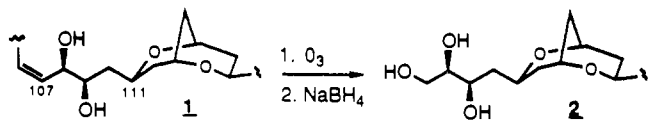
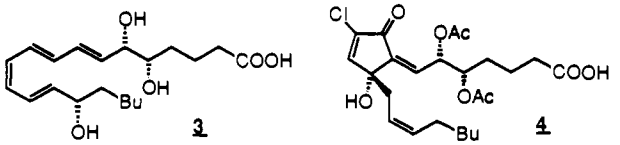
The assignment of stereochemistry in acyclic polyols by spectroscopic means remains a difficult task. Methods for assigning relative configuration in 1,3-polyols by NMR have recently emerged,[1-4] yet, of the over 200 1,3-polyhydroxylated polyene macrolides known,[5] only mycoticin A and B[6] have been fully assigned since the X-ray elucidation of amphotericin B.[7] In polyols with contiguous hydroxylation, such as those derived from palytoxin, the use of coupling constants to determine relative configuration proved unreliable.[8,9] As part of our efforts to develop circular dichroic methods for assignment of stereochemistry in acyclic polyols with multiple chiral centers,[4] we introduce here a general approach based upon the "bichromophoric" exciton chirality method[10-12] and report a simple procedure to assign both relative and absolute configuration in 1,2,3-triols.

Polyols are typically derived from a wide variety of natural products by either periodate or ozonolysis degradation, as was the case for palytoxin **1**,[8,13] which provided the 1,2,3-triol **2**. Ste-



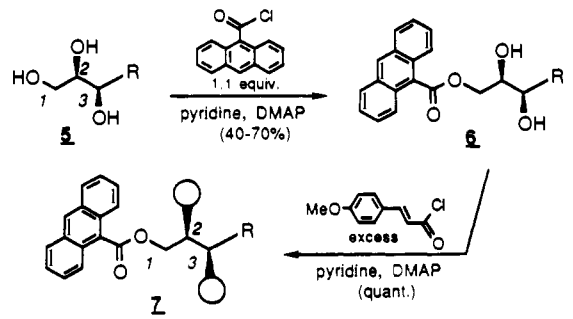
reochemical assignment of **2** and a second 1,2,3-triol fragment were achieved by asymmetric synthesis of the four possible stereoisomers of each.[13a] 1,2,3-Triols could be similarly derived from prostanoids such as lipoxin A (**3**) and punaglandin 4 (**4**). Stereochemical elucidations for these were achieved by total syntheses of all possible stereoisomers,[14,15] resulting in revision[15] of the originally proposed punaglandin structure.[16]



The exciton chirality method for CD spectroscopic determination of stereochemistry[17] has been most extensively applied in molecules with rigid ring systems, but applications to simple acyclic systems have also proven successful. Absolute configuration of acyclic allylic alcohols is easily determined by CD of the corresponding bromobenzoates,[18] and recently Harada reported that the CD curves of acyclic diols, derivatized as dibromobenzoates, can indicate stereochemistry at one or sometimes two chiral centers.[19]

The "bichromophoric" exciton chirality method[10,11] utilizes *two different types of exciton chromophores together* which have been selectively introduced at two different types of hydroxyls. Degenerate and nondegenerate exciton coupling interactions are superimposed to give "fingerprint" CD curves. In a preliminary study of acyclic triols and tetrols, selective 9-anthroylation of primary hydroxyls followed by per-*p*-methoxycinnamoylation of secondary hydroxyls provided CD spectra which clearly distinguished between stereoisomers.[12] We report here that this "bichromophoric" derivatization, applied to a series of acyclic 1,2,3-triols of known stereochemistry, results in CD curves which are *characteristic and predictable for each stereochemical pattern.* Thus, relative and absolute configuration of 1,2,3-triols can be deduced from a single measurement by using this simple spectroscopic method.

The acyclic triols, i.e., **5**, were obtained stereochemically pure from D sugars as dithioacetals[20] or hydrazinolysis products.[21] Treatment with 9-anthroyl chloride[22] afforded the 1-*O*-(9-anthroate) esters **6**[23] (λ_{max} 253 nm, ϵ 185 000). Subsequent



treatment of monoesters **6** with *p*-methoxycinnamoyl chloride[24]

† Dedicated to Günther Ohloff on the occasion of his 65th birthday.

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(23) Purified by flash chromatography ($MeOH/CH_2Cl_2$ 2:98, silica, 365 nm active) and characterized by ^1H NMR ($CDCl_3$, 250 MHz). For example, **6a** (R = Et): 8.51 (s, 1 H), 8.05-7.96 (m, 4 H), 7.56-7.44 (m, 4 H), 4.73 (dd, 4.6, 11.6 Hz, 1 H, H-1), 4.65 (dd, 6.6, 11.6 Hz, 1 H, H-1′), 3.93 (m, 1 H, H-2), 3.62 (m, 1 H, H-3), 1.7-1.5 (m, 2 H, CH_2), 0.98 (t, 7.4 Hz, Me).

(24) Prepared from the acid and thionyl chloride (1.2 equiv) in refluxing benzene (2 h). Benzene and excess reagent were removed in vacuo, and distillation in a sublimation apparatus (140 °C/0.1 mmHg) afforded the pure acid chloride.

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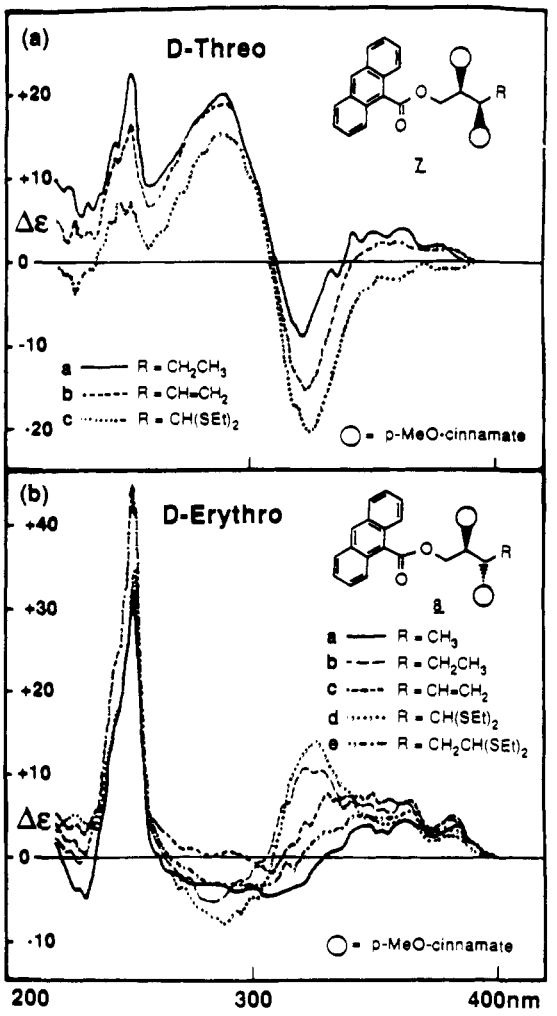

Figure 1. Circular dichroic spectra of "bichromophorically derivatized" 1,2,3-triols: Reference curves for empirical assignment of relative and absolute configuration.

gave the 1-*O*-(9-anthroate) 2,3-di-*O*-*p*-methoxycinnamates **7**.[25] The CD spectra[26] of these bichromophorically derivatized D-threo triols **7** are compared to the corresponding D-erythro derivatives **8**[27] in Figure 1. While both show positive Cotton effects at 253 nm indicating the *R* absolute configuration at C-2,[28] the magnitude of this Cotton effect in the erythro derivatives is roughly twice that in the threo derivatives. More dramatic differences between the two are seen at the 289 and 323 nm Cotton effects, which differ both in sign and magnitude. Variations within each group due to conformational differences (indicated by NMR coupling constants) are greatest when R is the bulky dithioacetal group (**7c** and **8d**, dotted lines).

The CD curves in Figure 1 may be used for empirical assignment of stereochemistry in 1,2,3-triols without any further understanding of the exciton coupling involved. We note, however, that they are in full accord with predictions based upon the recently demonstrated *pairwise additivity* of interchromophoric couplings.[10,11] CD curves of derivatives containing three or more chromophores can be accurately predicted by spectral summation of all two-chromophore subunits. Thus, these triol derivative spectra are accurately simulated by summation of the spectra corresponding to the 1,2- and 1,3-anthracene/cinnamate interactions and the 2,3-dicinnamate interaction,[29] indicating the nonempirical basis of the exciton chirality method.

This "bichromophoric" CD method has general applicability to a variety of hydroxylation patterns, including 1,3-polyols. We have completed an analogous study of 1,2,3,4-tetrols and 1,2,3,4,5-pentols and have found that up to four chiral centers can be assigned by this approach.[29] In addition to the exceptional ease with which this method can assign both relative and absolute configuration, it offers the distinct advantage of a minimal material requirement. The CD spectra are routinely recorded on 20 nmols or less, and the strongly fluorescent anthroate ester allows for derivatization and purification on a microscale (anthroate derivatives of hydroxysteroids have been prepared and chromatographed using fluorescent detection on μg quantities[22]). We are currently examining a range of applications to structural studies.

Acknowledgment. The studies have been supported by NIH Grant GM 34509.

(25) Purified by flash chromatography (CH_2Cl_2, silica, 365 nm active). Partial ^1H NMR data (CD_3CN): **7a**, 5.58 (ddd, 3.3, 4.5, 6.6 Hz, 1 H, H-2), 5.30 (ddd, 4.5, 5.1, 7.8 Hz, 1 H, H-3), 4.93 (dd, 3.3, 12.0 Hz, 1 H, H-1), 4.75 (dd, 6.6, 12.0 Hz, 1 H, H-1'); **7b**, 5.74 (dd, 5.8, 6.0 Hz, 1 H, H-3), 5.64 (ddd, 3.3, 5.8, 6.6 Hz, 1 H, H-2), 4.96 (dd, 3.3, 12.1 Hz, 1 H, H-1), 4.77 (6.6, 12.1 Hz, 1 H, H-1'); **7c**, (ref 12).

(26) CD spectra were recorded from 420-220 nm on a Jasco 500A spectropolarimeter using a 1-cm cell at ambient temperature. Acetonitrile solutions were prepared which were 5-15 μM, the exact concentrations determined from the UV extinction coefficients: anthroate monocinnamates ϵ_{311nm} = 28 400; anthroate dicinnamates ϵ_{311nm} = 49 400. Prior to UV and CD measurements, derivatives were purified by HPLC (EtOAc/hexane 3:7, YMC 5 μm SiO_2 gel column).

(27) Partial ^1H NMR data (CD_3CN): **8a**, 5.54 (ddd, 3.7, 4.9, 6.4 Hz, 1 H, H-2), 5.33 (dq, 4.9, 6.5 Hz, 1 H, H-3), 4.95 (dd, 3.7, 12.1 Hz, 1 H, H-1), 4.87 (dd, 6.4, 12.1 Hz, 1 H, H-1'); **8b**, 5.55 (ddd, 3.6, 4.6, 6.5 Hz, 1H, H-2), 5.27 (ddd, 4.4, 4.6, 8.2 Hz, 1 H, H-3), 4.95 (dd, 3.6, 12.1 Hz, 1 H, H-1), 4.88 (dd, 6.5, 12.1 Hz, 1 H, H-1'); **8c**, 5.71 (dd, 4.9, 6.0 Hz, 1 H, H-3), 5.62 (dt, 4.9, 5.1 Hz, 1 H, H-2), 4.90 (d, 5.1 Hz, 2 H, H-1's); **8d**, (ref 12); **8e**, 5.66 (ddd, 3.0, 4.2, 6.8 Hz, 1 H, H-3), 5.60 (ddd, 4.0, 4.2, 6.5 Hz, 1 H, H-2), 4.95-4.87 (m, 2 H, H-1's).

(28) Configurational assignments (*R*,*S*): **7a**,**b** and **8d**, (2*R*,3*R*); **8a**-**c**,**e** and **7c**: (2*R*,3*S*). Note that (*R*,*S*) assignments vary with alkyl substituent within each stereochemical family.

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Use of 2-D INEPT-INADEQUATE ^{29}Si NMR To Determine Structures of Organosilicon Rings

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Recently, it was found that Lewis acid catalyzed rearrangement of permethylcyclosilanes, $(SiMe_2)_n$, leads to branched cyclosilanes.[1] In each case a single isomer is formed. For $(SiMe_2)_n$ (n = 6-9), the rearranged products were all trimethylsilyl-substituted cyclopentasilanes; for n = 10 to 12, the rearranged compounds were trimethylsilyl-substituted cyclohexasilanes. However, the NMR spectra did not allow unambiguous structural assignments in all cases.[2,3]

We report here the first use of 2-D INEPT-INADEQUATE ^{29}Si NMR spectroscopy to establish the structures of two of the rearranged cyclosilanes. Although the INEPT-INADEQUATE pulse sequence has been developed previously for ^{13}C NMR,[4] and

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(3) To determine the most likely structure according to steric energies, MM2 calculations were performed on the likely structures, but this approach was also inconclusive because the calculations predict only small differences in energies between the isomers. For the product from $(SiMe_2)_8$ the difference in energy between the two most likely isomers **1** and **2** is 0.33 kcal mol^{-1}. The actual product **1** is predicted to be the more stable one. The steric energy difference in the two possible isomers **7** and **8** from the rearrangement of $(SiMe_2)_9$ is 4.14 kcal mol^{-1}, with the actual product **7** again predicted to be more stable.[2]
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