A Chiroptical/Chemical Strategy for Configurational Assignments of Acyclic 1,3-Skipped Polyols: Model 1,2,4,6-Tetrols

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In the following we present a microscale strategy for determining the relative and absolute configurations of acyclic 1,3-polyols up to 1,2,4,6-tetrols; extension of the same principle allows one to apply the method to pentols and longer 1,3-polyols.

The 1,3-polyol systems are widely distributed in nature, particularly in the skipped-polyol polyene macrolides which are very important as antifungal and antiviral agents. However, due to difficulties associated with configurational assignments, out of the >200 polyene macrolides isolated, most of which are amorphous, the planar structures of only ca. 40 have been determined.[1] Furthermore, the number of members to which full or partial stereochemistry has been assigned is less than 10:[1] amphotericin B (X-ray),[2] roxaticin (X-ray),[3] mycoticin (degradation and partial synthesis),[4] nystatin (degradation and spectroscopy),[5] and lienomycin (degradation and spectroscopy).[6]

Two reiterative methods have been published recently to assign configurations to the skipped polyols. According to Oishi and co-workers,[7] the steps consisting of lactonization between 1-COOH and 5-OH to 3-hydroxy-δ-lactone → NMR → dehydration to δ-enelactone → NMR give configurations at C-3/C-5/C-7; repetition of these steps after oxidative removal of C-1 to C-4 gives C-7/C-9/C-11 configurations. In the method of Mori et al.,[8] the difference CD between 1-hydroxy-3,5,...-perbenzoate and the corresponding allylic perbenzoate obtained upon 1,2-dehydration gives the absolute configuration at C-3 based on the sign of acyclic allylic benzoate CD;[9] the starting hydroxy perbenzoate is degraded to 3-hydroxy-5,7,...-perbenzoate, and CD measurements are repeated for the C-5 configuration.

The present method employs the bichromophoric[10] exciton chirality method[11] which was used in the microscale configurational determination of 1,2-polyols[12] (up to hexols, including 1-aminopentols). A combination of CD spectra of 1-anthroylated *p*-methoxycinnamates of the 1,3-polyols and the diastereoselective spiroketalization reaction of Oku and co-workers[13] has led to the following procedure.

The four possible diastereomeric tetrols **1–4** with established configurations, synthesized from (*S*)-(−)-malic acid,[14] served as models to develop the procedure. The absolute configuration at C-2 is first determined, thus decreasing the number of possible configurations in an unknown 1,2,4,6-tetrol from eight to four. This is achieved by selective derivatization with two different exciton coupling chromophores (Scheme I): C-1 anthroylation (λ_{max} 252 nm, ϵ 140 000) with 9-anthroylimidazole followed by per-*p*-methoxycinnamoylation (λ_{max} 306 nm, ϵ 23 400). The clear Cotton effect (CE)[15] at 252 nm results primarily from exciton coupling between the 1-Anth/2-Cinn chromophores;[10a,b,12] the contributions from the 1-Anth/4-Cinn and 1-Anth/6-Cinn couplets to the 252-nm band are much weaker and can be ignored. Thus a positive 252-nm CE in the 1-Anth-2,4,6-tricinnamate derivative is diagnostic for an *S*-configuration at C-2, its sign being independent of configurations at remaining chiral centers, and *vice versa*.

A strong bisignate CD around 300 nm, namely, a strong positive CE at 280 nm and negative CE at 320 nm (negative exciton coupling) is characteristic of two of the four possible structures, 2,4-*syn*-4,6-*anti* (**1a**) and 2,4-*anti*-4,6-*syn* (**2a**) (Figure 1a). This group will be denoted as "S" (for strong). An acyclic *anti*-1,3-dibenzoate adopts a planar zigzag form in its most stable conformer and exhibits a typical CD exciton couplet corresponding to the sign of the screw sense between the two gauche oriented chromophores.[16] However, in the most stable conformer of the *syn* analog, which is also zigzag, the transition moments of the acylate chromophores are parallel and hence show negligible coupling.[16] Thus, in **1a** and **2a**, the strong couplet arises from the coupling of the 4,6- and 2,4-*anti*-cinnamates, respectively; the 2,4-cinnamates in **1a** and 4,6-cinnamates in **2a** are *syn* and hence do not couple. In contrast, a weak CD in the 280–320-nm region is characteristic for configurations 2,4-*syn*-4,6-*syn* (**3a**) and 2,4-*anti*-4,6-*anti* (**4a**), denoted by group "W" (for weak) (Figure 1b). The coupling is weak in **3a** because the 2,4,6-cinnamates are all *syn*, whereas in **4a** the 2,4-*anti* and 4,6-*anti* contributions cancel out.

The differentiation between **1** and **2** of group S and **3** and **4** of group W becomes possible by using *l*-menthone, a highly diastereoselective reagent. According to Oku and co-workers,[13] *l*-menthone selectively spiroketalizes 1,3-*syn*-diols at −78 °C while leaving the 1,3-*anti*-diols unchanged. Both tetrols **1** and **2** reacted with *l*-menthone to give spiroketal derivatives **1b** and **2b** in agreement with their 2,4- and 4,6-*syn* configurations, respectively (Scheme I). With **1b**, cinnamoylation followed by deketalization gave **1c**, which exhibited only a weak CD throughout the region 220–360 nm because of the remoteness of the 1-Anth and 6-Cinn chromophores; the same two-step reaction applied to **2b** gave **2c**, which shows the strong positive 252-nm CE (Figure 1c). This differentiates **1** and **2** in group S. Treatment of tetrols **3** and **4** (group W) with *l*-menthone under the same conditions readily distinguished the two. Namely, **3** yielded two spiroketals **3b** and

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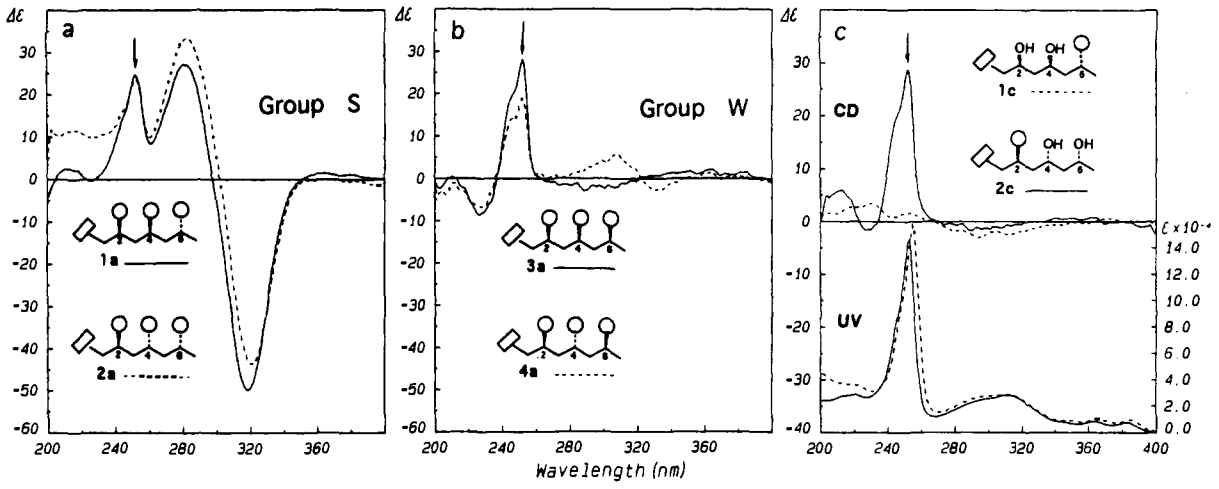
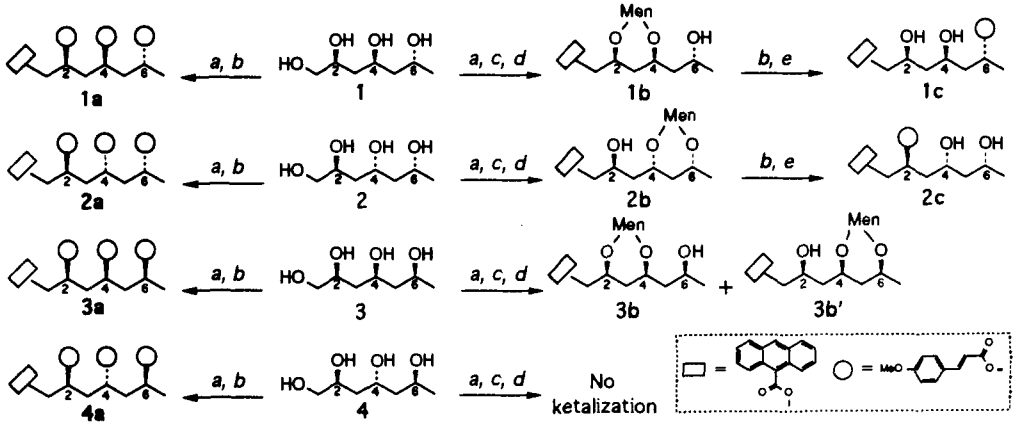


Figure 1. CD (λ_{ext} nm/$\Delta\epsilon$) and UV (λ_{max} nm/ϵ) spectra of derivatized tetrols in acetonitrile. (a) CD of **1a**: 252 ($\Delta\epsilon$ +24.7); 281 (+27.2); 319 (–49.8). CD of **2a**: 252 (+23.8); 283 (+33.3); 321 (–43.5). (b) CD of **3a**: 252 (+28.2); 289 (–3.0); 363 (+2.2). CD of **4a**: 252 (+19.0); 307 (+5.7); 330 (–2.7). (c) CD of **1c**: 252 (+1.6); 294 (–2.9); 311 (–2.4). CD of **2c**: 252 (+28.8); 296 (–1.4). UV of **1c**: 254 (ϵ 158 000); 309 (29 000) **2c**: 252 (147 000); 310 (28 000).

Scheme I. Chromophoric Derivatization and Ketalization of Tetrols **1–4**[a]



[a] (a) Anthroylation; (b) *p*-methoxycinnamoylation; (c) TMSCl, Et_3N; (d) *l*-menthone, TMSOTf, –78 °C; (e) MeOH, H^+.

3b′, whereas no reaction occurred with tetrol **4** having 2,4-*anti*-4,6-*anti*-configurations.

A typical procedure is as follows; although it was not attempted to minimize the amount of sample, the scale can readily be reduced to ca. one-tenth.[17]

(a) Peracylation of Tetrol, 1 → 1a. Treatment of tetrol **1** (10 mg) with 9-anthroyltetrazole[12b] (2 equiv) and DBU (2 equiv) in CH_2Cl_2 at room temperature (rt) for 3 h followed by silica gel chromatography gave the 1-anthroate,[17] 53% yield; further reaction with *p*-methoxycinnamoylimidazole[12b] (5 equiv) and DBU (4 equiv) in CH_3CN at rt for 4 h furnished **1a** in 85% yield.

(b) Spiroketalization, 1 → 1b. The tris-TMS derivative (11 mg) of the 1-anthroate of **1**, prepared by stirring of the anthroate with TMSCl (6 equiv) and excess Et_3N in dry CH_2Cl_2 (81%), was condensed with freshly distilled *l*-menthone (2 equiv) in THF at –78 °C for 14 h in the presence of TMSOTf (0.5 equiv). After the reaction was quenched by addition of pyridine at –40 °C, methanol was added at 0 °C and the reaction mixture was stirred for 1 h, 0 °C, to yield **1b** (92%) after silica gel chromatography.

(c) Cinnamolyation and Deketalization, 1b → 1c. Cinnamoylation of spiroketal **1b** (9 mg) under conditions described above with 1.5 equiv of *p*-methoxycinnamoylimidazole[12b] and 1.5 equiv of DBU furnished monocinnamoyl spiroketal (77%). Deprotection of **1b** in MeOH with a trace of CH_3COCl, rt, 2 h, yielded monocinnamoylated derivatives **1c** (65%).

(d) Separation of Ketals 3b and 3b′. The two were readily separable on silica gel column, **3b′** (40%) and **3b** (10%) being eluted, respectively, by 14% and 36% ether in hexane.

Acyclic 1,3-polyols with the α-glycol-terminal–CH_2–CHOH–CH_2OH are readily obtained from most polyene macrolides upon hydrolysis/reduction of the terminal –COOH coupled with ozonolysis. In the present method, the C-2 absolute configuration is determined from the 252-nm CD of the 1-anthroate per-*p*-methoxycinnamate; furthermore, depending on the *syn* or *anti* arrangements of the cinnamates, the 260–340-nm region shows a strong couplet or no couplet . Final determination of configurations is achieved by a spiroketalization step and, if necessary, cinnamoylation and deketalization. An advantage of the present method is that, unlike the method developed for 1,2-polyols,[10a,b,12] reference CD curves are not necessary. This communication is restricted to a description of the strategic principle rather than an application to a real case since none of the macrolides with established structures[1-5] possesses the tetrol moiety discussed above. However, extension of the strategy to acyclic pentols and mixed 1,2/1,3-polyol systems will be reported shortly with applications to real cases.

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(17) The purity and identity of all samples were checked by MS and ^1H NMR.