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Remarkably large remote-stereocenter-induced chromatographic differences: azulenyl 1,5-diols

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ABSTRACT

A series of four new azulene-1,5-diol diastereomers were prepared and found to exhibit large differences (ΔR_f 0.22–0.46) in silica TLC mobilities despite having stereocenters four bonds apart. The stereoisomers were identified by X-ray crystallography, and in all cases the RR/SS diastereomers were less strongly retained than the RS/SR diastereomers. The crystal structures suggested that this is due to a conformational preference for the CF_3 groups to be nearly perpendicular to the plane of the azulene ring, which caused the dihedral angle between the OH groups to be larger (in the RR/SS diastereomers) or smaller (in the RS/SR diastereomers). The smaller dihedral angles allow the RS/SR diastereomers to simultaneously bind to a silica surface and thus be more strongly retained. Two similar benzene derivatives and several cycloalkanediols with more proximate stereocenters showed little or no difference in mobilities between diastereomers, though the NMR differences were greater. Thus, the azulene ring is an important factor in enforcing the conformational preferences, either through steric interactions with the 4/8 substituents (H or methyl) or its significant dipole moment, or both.

Introduction

In general, diastereomers in which chiral centers are separated by one or more carbons tend to have very similar properties, such as chromatographic mobility and NMR chemical shifts. The factors that influence the chromatographic separation of diastereomers remain poorly understood, but the proximity of stereogenic centers is typically of major importance. Diastereomers with chiral centers more than four bonds apart have been considered to be inseparable,[1] though in some cases diastereomer ratios can be determined by NMR even with less proximate stereocenters.[1,2] During explorations to identify a challenging column chromatography separation of colored compounds in an undergraduate advanced organic laboratory, we were surprised to observe that the diastereomers of 1,5-diol **1** exhibited dramatically different mobility on silica TLC (ΔR_f >0.4) despite having stereocenters separated by four bonds. We proceeded to seek the causes of this remarkable difference in R_f values by studying other azulene diols (**2**–**4**), related benzene compounds (**5**, **6**), (Fig. 1) and several cycloalkane diols (Fig. 2).

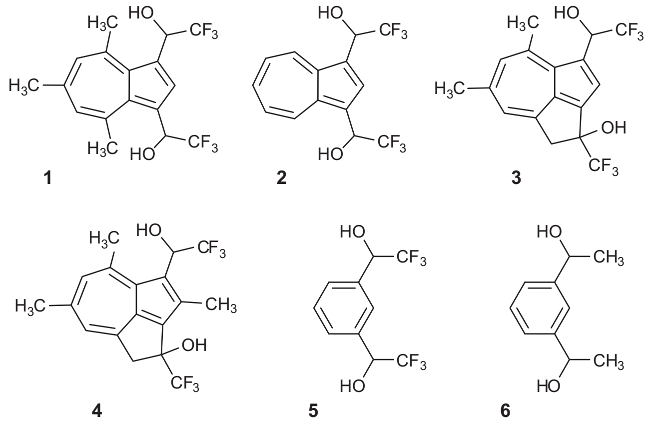

Figure 1. Azulene- and benzene-diol diastereomers studied.

Results and discussion

Synthesis of azulene and benzene 1,5-diols

Azulene diols are unknown in the literature; none of the compounds **1**–**4** have been reported previously. All of these diols were

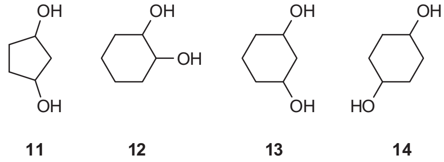

Figure 2. Cycloalkanediol diastereomers studied.

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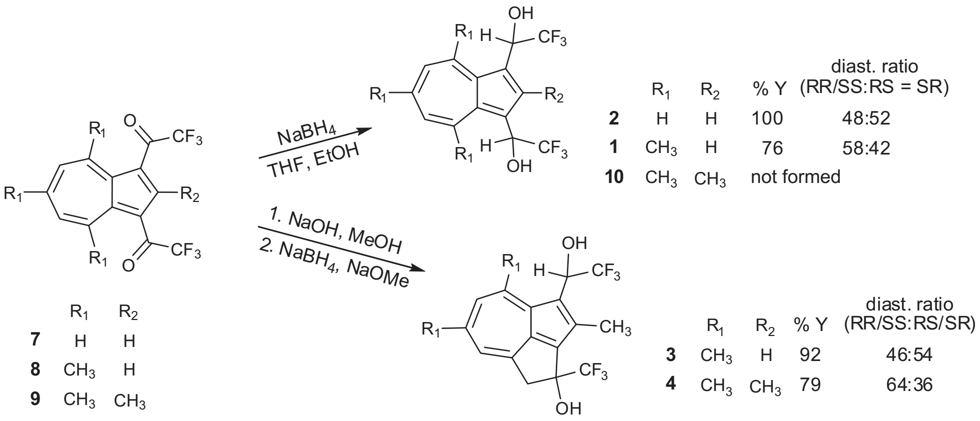

Scheme 1. Preparation of azulene-1,5-diols.

prepared by borohydride reduction of the corresponding ketones, though in the tricyclic cases (**3**, **4**) the tertiary hydroxyl was the result of a known[3,4] cyclization. The known[3–5] diketones (**7**, **8**, and **9**) were prepared by bis-trifluoroacylation of azulene, 4,6,8-trimethylazulene,[6] and 2,4,6,8-tetramethylazulene[3] with excess trifluoroacetic anhydride. Except in the case of diketone **9**, reduction of the red/orange diketones with NaBH$_4$ in ethanol/THF generally provided the purple or lavender diol diastereomers efficiently (Scheme 1). The tricyclic compound **3** was first prepared in low yield (12%) by treatment of diketone **8** with excess LDA; the first equivalent caused cyclization,[3] and the second equivalent caused the reduction.[7] We found that NaOH in methanol efficiently afforded monocyclization. However, bis-cyclization was not possible under any conditions we could identify. Subsequent reduction with NaBH$_4$ yielded the diol diastereomers **3** and **4** in good yields. Yields and diastereomer ratios are given in Scheme 1, with stereochemical assignments made as described below.

Rather inexplicably, under a variety of reduction conditions (borohydride, triethylborohydride, NaBH(OAc)$_3$, LAH), including Shvo's catalyst/H$_2$,[8] the tetramethylazulene diketone **9** gave only complex reaction mixtures in which the desired diols **10** were not evident. Also 1,3-diacetylazulenes (i.e., methyl rather than trifluoromethyl ketones) could not be reduced to the corresponding diols; very messy mixtures resulted instead. We believe the latter observation is related to the strong tendency of azulenes to stabilize cations adjacent to the azulene 1 and 3 positions as aromatic tropilium cations. The reduction of acetylazulenes has been reported only twice,[9a,b] and instability of the resulting alcohol was noted.[9b]

The benzene derivative **5** was prepared in 57% yield by the known[10] fluoride-promoted addition of TMS-CF$_3$ to isophthalaldehyde. Derivative **6** was prepared by borohydride reduction of the commercially available 1,3-diacetylbenzene to form the known diol.[11]

Cycloalkanediols **11**–**14** (Fig. 2) were synthesized by hydrogenation of the corresponding diketones with the commercially available Shvo's ruthenium catalyst[8] to efficiently give mixtures of the diol diastereomers. In contrast, borohydride reduction of the diketones gave complex intractable mixtures.

Stereochemistry and separability of diastereomers

The diastereomers were easily separated by silica column chromatography using 10% ethyl acetate in dichloromethane. X-ray crystallography revealed a consistent stereochemical relation between all of the azulene diols and their chromatographic mobilities on silica gel. Careful recrystallization provided X-ray quality crystals of the faster-moving diastereomers of diols **2**, **3**, and **4**, and the slower-moving diastereomers of diols **1** and **3**. This consistently showed the faster moving diastereomer to have the (RR)/(SS) stereochemistry, and the slower moving diastereomer to have the (RS)/(SR) configuration. For diols **1** and **2**, the slower-moving diastereomer is a meso stereoisomer.

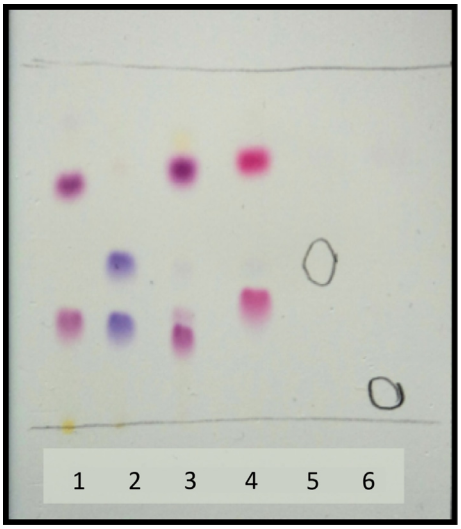

Figure 3. Photograph of diastereomeric separation on a silica thin layer silica chromatography plate using 25% ethyl acetate in DCM as the eluting solvent.

All of the azulene diols exhibited rather large differences in mobility on silica TLC (ΔR_f 0.22–0.46) in DCM-based mobile phases (Fig. 3), and lesser separations (ΔR_f 0.10–0.28) in 25% ethyl acetate in hexanes, as noted in Table 1. Diastereomeric differences in GC were more modest, and only small differences were evident by NMR. In contrast, the benzene derivatives (**5**, **6**) showed no chromatographic differences by TLC or GC, and only slight differences in the NMR spectra. Remarkably, even a series of 1,2-, 1,3- and 1,4-cycloalkanediols (**11**–**14**) showed no TLC differences, except diol **11** ($\Delta R_f \sim 0.02$), despite having more proximate functional groups. However, the cycloalkanediols did exhibit much more substantial differences in both ^{1}H and ^{13}C NMR than the azulene or benzene diols. This was especially prominent in the cycloalkanediols containing chiral centers that were only 1 or 2 bonds apart.

Origin of the diastereomeric differences

The X-ray structures revealed that there was a correlation between the stereochemistry and polarity (Fig. 4). The dihedral angle between the two C–O bonds (Table 2) was significantly greater