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1,3-Dipolar Addition of Diazomethane to 1-Acetoxy-2-hydroxycyclohexa-3,5-diene. Synthesis of a Couple of Chiral Δ^1-Pyrazolines.

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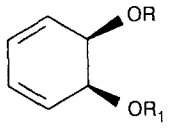
Abstract: The 1,3-dipolar addition of diazomethane to (1*R*)-acetoxy-(2*S*)-hydroxy-3,5-hexadiene **2** takes place with complete facial selectivity to give two diastereoisomeric Δ^1-pyrazolines, **3** and **4**, in a 3:1 ratio. This is the first example of this type of reaction on a cyclohexa-3,5-diene-1,2-diol derivative. Photochemical decomposition of **3** affords the cyclopropyl derivative **7**, which retains the stereochemistry of the parent compound.

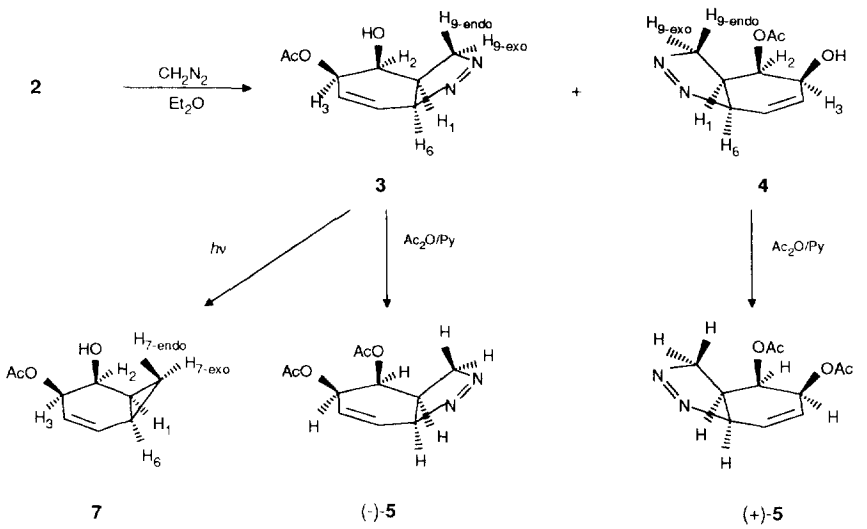
Gibson's pioneering work on the microbial oxidation of arenes[1] opened up a productive course of research which has led to the development of the production of arene *cis*-dihydrodiols, of which several are now commercially available. This family of compounds soon acquired a pivotal role as starting materials for the synthesis of a variety of natural products and molecules of biological or pharmacological interest.[2] In fact, due to the presence of the double bonds, arene *cis*-dihydrodiols can participate in many different reactions, for instance electrophilic additions, Diels-Alder cycloadditions and [2+2]cycloadditions.[3] The simplest member of the family, 1,2-dihydroxycyclohexa-3,5-diene ("benzene *cis*-glycol", **1**) is also amenable to the synthesis of a number of important compounds, but unfortunately owing to its symmetrical (*meso*) structure in reactions with achiral reagents it yields racemates, which require the application of resolution methodology for the preparation of enantiomerically pure compounds. A more direct route to homochiral synthetic targets is the asymmetrization of **1** , for instance by enantiotoposelective derivatization of one of the hydroxyl groups. However, the (apparent) instability of such compounds, typified by monoacetate **2** which is sensitive toward acid-catalysed elimination to yield phenol, was considered a serious obstacle. The recent finding from our group that **2** can be prepared easily[4] and that it is reasonably stable for manipulation without particular difficulties prompted us to examine its chemical behaviour particularly from the viewpoint of regio- and stereoselectivity. Moreover, to extend the utility of **2** in the preparation of potentially useful compounds, we decided to study its reactivity toward 1,3-dipolar reagents. In the present work we wish to describe the reaction of **2** with the oldest and most studied 1,3-dipole, diazomethane, to give two isomeric Δ^1-pyrazolines, **3** and **4**.



1 R=R$_1$=H
2 R=Ac R$_1$=H
6 R=R$_1$=Ac

Diazomethane reacted with **2** to furnish the Δ^1-pyrazolines **3** and **4** in a 3:1 ratio, as calculated by ^{1}H-NMR analysis of the whole reaction mixture. The optically active **3** was clearly a Δ^1-pyrazoline, as evidenced by the band at ν 1531 cm^{-1} (–N=N– stretching) in the IR spectrum and the resonance at δ 77.8 for the C$_9$

methylene in the ^{13}C NMR spectrum. Its gross structure was determined by the analysis of the ^{1}H-NMR spectrum with the aid of 2D-COSY. Aside from the signal for the acetate protons, the spectrum contained eight distinct resonances, among which of crucial importance were those relative to the bridgehead methines: in fact, the signal for H_1 was a double double double doublet due to vicinal couplings with H_2, H6, $H_{9\text{-endo}}$ and $H_{9\text{-exo}}$ while H_6 appeared as a complex multiplet coupled vicinally with H_1 and H_5, allylically with H_4, homoallylically with H_3 and through five bonds over the –N=N– bridge[5] with $H_{9\text{-endo}}$ and $H_{9\text{-exo}}$. The stereochemistry at the stereogenic centres C_1 and C_6 was assigned on the basis of the following considerations: i) the values of chemical shift for $H_{9\text{-endo}}$ and $H_{9\text{-exo}}$ are largely different (0.75 ppm), as expected for protons in significantly different chemical environment generated by *syn* substituents;[6] ii) H_1, H_6 and $H_{9\text{-exo}}$ are on the same face of the



molecule, as can be deduced from the values of the coupling constants $J_{1\text{-}6}$=8.6 and $J_{1\text{-}9exo}$=8.7 Hz; iii) the change of the solvent from $CDCl_3$ to C_6H_6 caused a comparable upfield shift for all the protons but $H_{9\text{-endo}}$, which is less prone to solvation due to the shielding by the *syn* substituents;[7] iv) the presence in the NOESY spectrum of H_1-H_3 and H_1-H_2 cross peaks.

The stereostructure of the minor adduct **4** can be immediately defined from the observation that its acetylation yielded a diacetate spectroscopically indistinguishable from that obtained from **3**, but with the opposite sign of specific rotation. The spectral properties of **4** (the ^{1}H-NMR spectrum is shown in Figure 1) are commensurate with the assigned structure.

From the data above it can be concluded that diazomethane in the reaction with **2** preferentially attacks the C_3 over the C_5 double bond, however in both cases with complete *syn* facial selectivity. A possible explanation of this behaviour, which is analogous to that observed for cyclobutenes bearing allylic substituents containing heteroatoms, is the one proposed by Franck-Neumann and Sedati[8] who invoked a σ^* (of the allylic substituents)-π stabilizing interaction in the activated complex.

The same reaction carried out on the *meso*-compounds **1** and **6** had an analogous course and gave the corresponding pyrazolines, obviously as racemates. The observation that **6** reacts with diazomethane faster than **1** indicates that steric hindrance does not play a relevant role in determining the regioselectivity in the reaction with **2.**

Photochemical decomposition of **3** occurred with retention of the stereochemistry to afford the *syn* cyclopropyl derivative **7**. This reaction can be of preparative value, since carbene addition reactions involving related substrates lead to products in which the cyclopropane ring is *anti* to the oxygen functions.[9]

EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded at 250.13 and 62.9 MHz on an AC 250 Bruker spectrometer in $CDCl_3$ solution, unless otherwise stated. Chemical shifts are reported in ppm (δ) downfield from TMS and coupling constants (J) are given in Hz. 2D COSY and NOESY experiments were performed using standard Bruker microprograms. Optical rotations were measured on a DIP 135 JASCO instrument.
Melting points are uncorrected. Mass spectra were obtained at 70 eV on a Kratos MS-50 spectrometer. Diazomethane was prepared by sodium hydroxide treatment of *p*-tolylsulfonylmethylnitrosoamide (Diazald, Aldrich). Compound **2** was available from previous work on the enantiotoposelective acetylation of **1** catalysed by immobilised lipase from *Mucor miehei* (Lipozyme® IM, Novo Nordisk) in *tert*-butyl methyl ether.[4] Since this monoester shares with **1** a remarkable tendency to aromatize, to avoid severe losses in the purification procedures we used the crude product (>95% ee) containing about 10% of diester **6**.

Reaction of 2 with diazomethane to give 3 and 4. An ethereal solution of diazomethane was added to a solution of **2** (280 mg, 1.8 mmol) in *tert*-butyl methyl ether and the resulting mixture was kept at room temperature. At the 4th h, ^1H-NMR analysis of a small aliquot of the reaction mixture indicated a conversion near 50% and a 3:1 ratio between the two diastereomers **3** and **4.** After additional 20 h the crystalline precipitate of chromatographically pure **3** (104 mg) was collected by filtration and the mother liquors taken to dryness to give a residue which by repeated recrystallization from *tert*-butyl methyl ether/CH_2Cl_2 (1:1 v/v) gave an additional amount of **3** (51 mg) and 51 mg of **4**.
Compound 3: (179 mg, 54% yield), $[\alpha]_D$ –231 (*c* 0.62, $CHCl_3$), mp 136. EI-MS: *m/z* (%) 196 (81), 154 (12), 136 (40), 135 (69), 119 (100), 118 (46). 107 (46). ^1H NMR (Δδ=δ $CDCl_3$–δ C_6D_6): δ 6.76 (ddd, H_5, $J_{5\text{-}4}$=10.2, $J_{5\text{-}6}$=3.5, $J_{5\text{-}3}$=2.4, Δδ 0.31), 5.71 (m, H_4, Δδ 0.35), 5.30 (m, H_3, Δδ 0.30), 5.00 (ddd, $H_{9\text{-endo}}$, $J_{9endo\text{-}9exo}$=17.3, $J_{9endo\text{-}1}$=2.3, $J_{9endo\text{-}6}$=2.2, Δδ 0.27), 4.5 (m, H_6, Δδ 0.7), 4.25 (ddd, $H_{9\text{-exo}}$, $J_{9exo\text{-}9endo}$=17.3, $J_{9exo\text{-}1}$=8.7, $J_{9exo\text{-}6}$=3.1, Δδ 0.65), 3.86 (m, H_2, Δδ 0.56), 2.50 (dddd, H_1, $J_{1\text{-}6}$=8.6, $J_{1\text{-}9exo}$=8.7, $J_{1\text{-}9endo}$=2.3, $J_{1\text{-}2}$=3.5, Δδ 1.11), 2.10, (s, CH_3CO-, Δδ 0.55). ^{13}C NMR: δ 21.07, 32.90, 65.50, 70.81, 77.81, 83.80, 125.88, 126.68, 172.10. IR ($CHCl_3$) 1740, 1531 cm^{-1}.
Compound 4: (51 mg, 15.4% yield), $[\alpha]_D$ +218 (*c* 0.60, $CHCl_3$), mp 153. EI-MS: *m/z* 196 (96), 154 (32), 136 (40), 135 (100), 119 (53), 108 (80). ^1H NMR: δ 6.64 (ddd, H_5, $J_{5\text{-}4}$=10.2, $J_{5\text{-}6}$=3.1, $J_{5\text{-}3}$=2.3 Hz), 5.84 (m, H_4), 5.14 (m, H_2), 4.77 (ddd, $H_{9\text{-endo}}$, $J_{9endo\text{-}9exo}$=17.6, $J_{9endo\text{-}1}$=2.1, $J_{9endo\text{-}6}$=2.1 Hz), 4.50 (m, H_6), 4.35 (m, H_3), 4.21 (ddd, $H_{9\text{-exo}}$, $J_{9exo\text{-}9endo}$=17.6, $J_{9exo\text{-}1}$=8.6, $J_{9exo\text{-}6}$=3.0 Hz), 2.58 (dddd, H_1, $J_{1\text{-}6}$=8.7, $J_{1\text{-}9exo}$=8.6, $J_{1\text{-}9endo}$=2.1, $J_{1\text{-}2}$=3.7), 2.08 (d, OH, J=5.8), 2.00 (s, CH_3CO-). ^{13}C NMR: δ 20.91, 32.00, 66.72, 69.70. 77.71, 84.13, 123.64, 130.78, 171.78.

Acetylation of 3 and 4. Compound **3** (100mg) was dissolved in CH_2Cl_2 (2mL) and treated with pyridine (0.2 mL) and Ac_2O (0.2 mL), and the mixture kept at room temperature for 24 h. Conventional workup gave the pure acetate (–)-**5** (110 mg, 90% yield), $[\alpha]_D$ – 97 (*c* 1, $CHCl_3$). ^1H NMR: δ 6.72 (ddd, H_5, $J_{5\text{-}4}$=10.2, $J_{5\text{-}6}$=3.8, $J_{5\text{-}3}$=3.3), 5.77 (m, H_4), 5.35 (m, H_3), 5.23 (m, H_2), 4.69 (ddd, $H_{9\text{-endo}}$, $J_{9endo\text{-}9exo}$=17.5, $J_{9endo\text{-}1}$=2.1, $J_{9endo\text{-}6}$=2.0), 4.56 (m, H_6), 4.20 (ddd, $H_{9\text{-exo}}$, $J_{9exo\text{-}9endo}$=17.5, $J_{9exo\text{-}1}$=8.6, $J_{9exo\text{-}6}$=3.0), 2.63 (dddd, H_1, $J_{1\text{-}6}$=9.1, $J_{1\text{-}9exo}$=8.6, $J_{1\text{-}2}$=4.0, $J_{1\text{-}9endo}$=2.1), 2.01 (s, CH_3CO-), 1.97 (s, CH_3CO-). In the same conditions **4** afforded a compound which had the same spectral properties but opposite sign of optical rotation, $[\alpha]_D$ +95.3 (*c* 1,$CHCl_3$).

Reaction of 1 and 6 with diazomethane. Ethereal solution of diazomethane was added to separate solutions of **1** and **6** (1.8 mmol) in *tert*-butyl methyl ether and the mixtures were kept at room temperature. After 4 h, ^1H NMR analysis of the crude reaction mixtures indicated a 45% conversion of **1** and 70% conversion of **6** in the corresponding pyrazoline derivatives.

Photochemical decomposition of 3. A solution of the compound **3** (50 mg) in of $CHCl_3$ (25 mL) was placed in a Pyrex tube and irradiated by sun-lamp (range 310-390 nm) for 15 min until all the pyrazoline was destroyed. The evaporation of the solvent *in vacuo* gave 35 mg (82% yield) of **7**, $[\alpha]_D$ −315 (*c* 0.23, $CHCl_3$). ^1H NMR (C_6D_6) δ 5.98 (dd, H_5, J_{5-4}=9.5, J_{5-6}=5.2), 5.50 (dd, H_4, J_{5-4}=9.5, J_{4-3}=6.1), 5.37 (ddd, H_3, J_{3-4}=6.1, J_{3-2}=5.3, J_{3-1}=1.6 Hz), 4.04 (t, H_2, J=5.5), 1.55 (s, CH_3CO-), 1.24 (m, H_1), 1.05 (m, H_6), 0.92 (m, $H_{7\text{-endo}}$), 0.63 (ddd, $H_{7\text{-exo}}$, J=3.9, 8.4 and 8.5). ^{13}C NMR (C_6D_6) δ 13.48, 16.07, 16.86, 20.57, 66.72 , 69.05, 120.38, 136.06, 170.24.

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