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Synthesis of (R,R) and (S,S) Bicyclo[3.3.0]octane-2,6-dione Interactions Between Non-Conjugated Chromophores

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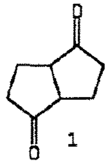
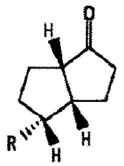
Abstract : Optically pure bicyclo[3.3.0]octane-2,6-dione is easily obtained with a yield of 4% for each enantiomer from 1,5-cyclooctadiene in 5 steps, by resolution of the intermediate diol with menthyloxyacetic acid. Its CD is 60 % larger than twice the CD of a corresponding monoketone indicating interactions between non-conjugated chromophores.

Interactions between non conjugated chromophores have been characterized in bicyclo[3.3.0]octane-2,6-dione **1** by ^{13}C nuclear magnetic resonance (NMR)[1]. Similar interactions have also been observed by chiroptical methods, optical rotatory dispersion (ORD)[2] and circular dichroism (CD)[3], when the Cotton effect ($\Delta\varepsilon$ in CD or amplitude a in ORD) is larger than the sum of the Cotton effects of the corresponding monoketonic moeities[2], the UV spectrum being only weakly perturbed. Since diketone 1 has C_2 symmetry, it may be expected that the previously reported interactions could also be observed by chiroptical methods.

Optically active diketone **1** and monoketonic derivatives **2** have been prepared[4-6] in various degrees of optical purity and their absolute configuration established by chemical correlation[7], NMR[6] and CD[5].



1



2a R=H
2b R=OH

[(1S,5S) **1**: 88% ee, $[\alpha]_D$ (corr. for 100% ee) = +401 (c=2, EtOH)[4] ; (1R,5R) **2a**: 100% ee, $[\alpha]_D$ = -105 (c = 3, $CHCl_3$)[5] ; 76% ee, $[\alpha]_D$corr. = -87 (c=3, $CDCl_3$)[4] ; (1S,2R,5S) **2b** : 99% ee, $[\alpha]_D$ = +103 (c=1.4, $CHCl_3$)[6]].

Their ORD data have been published[3,4]. As shown in figure 1, the ORD of diketone **1** (1S,5S)[4] (corrected for 100% optical purity) is larger than twice the ORD of monoketone **2a** (1R,5R) (optically pure or corrected to 100% optical purity). Unfortunately, this data does not permit the determination of the corresponding amplitude a.

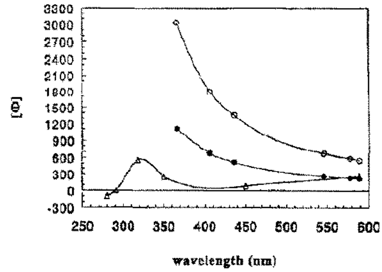
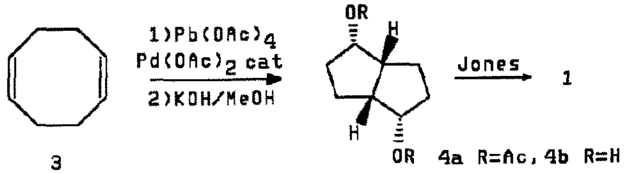


Figure 1 : Optical rotatory dispersion of
1 (EtOH) : o—o—o (ref. 3)
2a ($CDCl_3$) : ●—●—● (ref. 3)
2a ($CHCl_3$) : Δ—Δ—Δ (ref. 4)
(corrected for 100% optical purity)

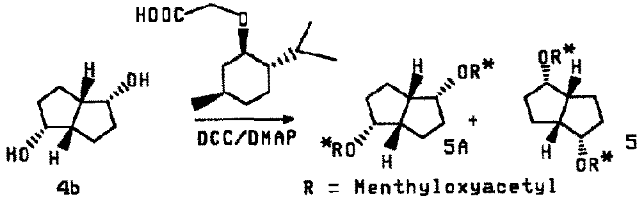
Since enantiomerically pure diketone **1** could be a useful synthon[8-11], we thought it would be worthwhile to develop an expedient chemical way to obtain both enantiomers. This could allow us to measure its CD and compare it to the CD of monoketonic derivatives. A combination of several reported procedures was choosen[10,12,13] (alternatively 1 is accessible via an other synthesis[14]) :



Thus, 1,5-cyclooctadiene **3** (6.6g) was treated for 36 hours with catalytic amounts of $Pd(OAc)_2$ (400mg, 0.02 eq) in the presence of 1M $Pb(OAc)_4$ (39g) in acetic acid at room temperature. The main product was the di*endo* diastereoisomer **4a** (8.5g 63%, colourless crystals, from pentane, mp 40°C, lit[9] 36°C). Saponification of **4a** (1.43g in 5 ml of MeOH) (KOH:MeOH 1.33M (4 ml) , 45min 0°C, then 30min 20°C) gave 0.8g of the di*endo* diol **4b** (90%, colourless oil)[11], 0.85g oxidized to dione **1** (0.6g, 70%) (Jones reagent (2.7M), acetone (20ml), 1h 0°C, 15h rt) (mp 45°C, lit[12]45-46°C). The use of palladium acetate suppresses the formation of 6-*exo*-chloro-2-*endo*-acetoxy[3.3.0] octane, a by-product of the palladium chloride catalysed reaction[15].

Attempts to resolve directly the dione by inclusion in β-cyclodextrin , in 1,6-*bis*-(2-chlorophenyl)-1,6-diphenyl-2,4-hexadiyne-1,6-diol, or via covalent derivatives with dimethyl tartrate or (S)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) failed. The resolution was done on diol **4b**. Esterification of **4b** (1.7g) with (-) menthyloxyacetic acid (5.5g) (DCC (5.8g)/DMAP (0.3g), diethyl ether, 2h 0°C, 15h rt) (scheme 1) gave a mixture of the two diastereoisomers **5A** and **5B** (5g, 78%, after chromatography on SiO_2, pentane/ether (8:2)). After two recrystallisations in pentane, an optically pure product[16] **5A** (15%) was obtained. Its optical purity (99%) was confirmed by differential scanning calorimetry (DSC)[17]. Saponification of **5A** (0.35g in 2ml MeOH) (KOH/MeOH (0.34 M, 3ml), 90%), gives (1S,2R,5S,6R) **4b** (85mg), $[\alpha]_D = -39$ (c=0.5, $CHCl_3$), lit[4] : $[\alpha]_D = -48$ (c=2, $CHCl_3$); vapor phase chromatography of its corresponding o-acetyllactyldiester[18] shows an enantiomeric excess greater than 99%. 4b was oxidized as previously to afford the dione (1S,5S) **1** (50-70%, colourless needles, mp 43°C; $[\alpha]_D = +394$ (c=0.25, EtOH), $[\alpha]_D = +474$ (c=0.05, CH_2Cl_2), lit[4] $[\alpha]_D = +401$ (c=2, EtOH)). (+) Menthyloxyacetic acid gave the dione (1R,5R) **1**, $[\alpha]_D = -457$ (c=1, CH_2Cl_2).

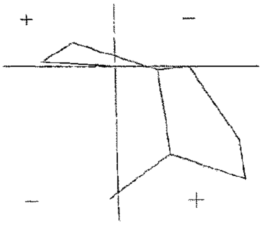
Scheme 1



Monoketonealcohol **2b** (*endo*-2-hydroxy-6-oxobicyclo[3.3.0]octane) was prepared by enzymatic reduction[19] (7 days, rt) with horse liver alcool deshydrogenase (HLADH) (12mg, 2U/mg) of **1** (40mg), 11mg were obtained (30%, colourless oil[20], $[\alpha]_D = +113$ (c = 0.35, $CHCl_3$), lit[6] for (1S,2R,5S) **2b**:

$[\alpha]_D = +103$ (c = 1.38, $CHCl_3$)). It has a $\Delta\varepsilon = 1.4\ M^{-1}cm^{-1}$ in CH_2Cl_2. Figure 2 shows the octant diagram of (1S,2R,5S) **2b** obtained after energy minimization[21] : this leads to a positive Cotton effect in full agreement with experiments.

Figure 2 :
Octant diagram of **2b**



We are now in a position to compare the circular dichroism of diketone **1** and its monoketonic derivative **2b**. The UV absorption of 1 (fig. 3) shows a hypsochromic shift relative to **2b** from 302 nm to 292 nm ($\Delta\nu = 1134\ cm^{-1}$), ε of the diketone **1** being almost exactly twice that of the monoketone **2b**. Its CD is much larger than twice the CD of **2b** (fig. 4). Without any interaction between chromophores, we could expect a Δε of 2.8 $M^{-1}\ cm^{-1}$ for (1S,5S) **1** in CH_2Cl_2. The measured value ($\Delta\varepsilon = 4.671\ M^{-1}\ cm^{-1}$) is larger by 60%. This large increase can be taken as a manifestation in the CD of the effect previously detected in **1** by ^{13}C NMR[1]. The 1134 cm^{-1} shift in the UV absorption may be taken as the order of magnitude of the splittings of the n and π^* levels[22] in diketone **1**. It is probable that a quantitative treatment of these interactions should also take into account the C_2 symmetry of **1**.

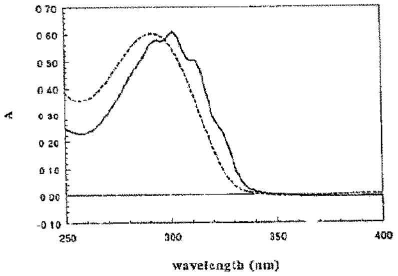


Figure 3 : UV spectrum of **2b** : ---------
and of **1** : ——— in CH_2Cl_2,
(molar concentration of **2b** is twice that of **1**)
(ε of 1 = 46 ; ε of **2b** = 23)

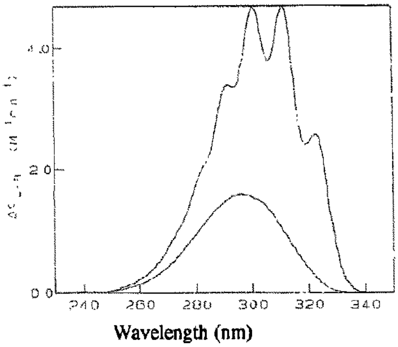


Figure 4 : Circular Dichroism of monoketone **2b**, diketone **1** in CH_2Cl_2

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16. ^1H NMR ($CDCl_3$, 250MHz, d ppm) : 0.8 (m, d, J=7Hz; 8H), 0.9 (m, dd, 16H), 1.3 (m, 4H), 1.6 (m, 8H), 1.75(m, 4H), 2.05 (m, 2H), 2.3 (m, 2H), 2.75(m, 2H), 3.15 (m, 2H), 4.1(dd AB J=16Hz), 5.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9MHz, d ppm) : 16.22(q), 20.09 (q), 22.2 (q), 22.7 (t), 23.2 (t), 25.4 (d), 31.4 (d), 32.1 (t), 34.3 (t), 39.9 (t), 44.6 (d), 48 (d), 66 (t), 77.4 (d), 80.2 (d), 170.4 (s); F=84.24°C (DSC); $[\alpha]_D = -129.7$ (c=0.15, CH_2Cl_2)

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20. ^{13}C NMR ($CDCl_3$, 62.9MHz, d ppm) : 20.05 (t), 25.15 (t), 35.09 (t), 38.40 (t), 45.73 (d), 50.44 (d), 75.64 (d), 223.69 (s)

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