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Unusual Rearrangements in Cage Compounds Due To Proximity Effects[1]

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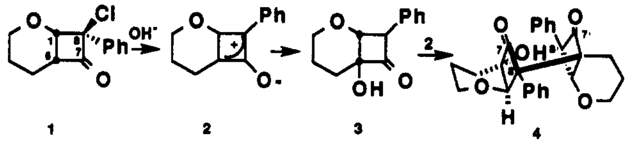
The strained keto diol **5** underwent an unexpected rearrangement in the presence of H_2O–TEA–CH_3CN at 20 °C to afford two isomeric products **6** and **7**. The latter two compounds undergo further conversion to carboxy keto diol **8**. The structures of **6**–**8** were elucidated by heterero COSY experiments and in the case of **6** by X-ray diffraction. The transformation of **5** to **6** and **7** is interpreted as involving an unusual retroaddition of a benzylic anion to a cyclobutanone **5**→**10**. This is facilitated by subsequent readdition of this anion to another proximally located ketone with formation of a cyclopropanol **11**, which is immediately converted to **6** and **7**.

Recently we have shown[2] that chlorobicyclooctanone **1** underwent with a variety of nucleophiles a cine substitution[3] reaction which proceeded via oxidoallyl cations,[4] (e.g. **1**→**2**→**3**). When the nucleophile was hydroxide ion (H_2O–Et_3N, CH_3CN, 20 °C), the enolate of the cine substitution product **3** competed for the oxidoallyl cation **2** to produce as primary products two diastereoisomeric dimers.[5] The major of these diastereomers was diketo alcohol **4**, which reacted further at room temperature within minutes due to proximity effects (see **9**) to afford the novel strained cage compound **5**. The latter was identified as a keto diether diol, possessing two rather strained cyclobutane rings. A kinetic study by NMR of the reaction of **1** had revealed[5] that product **5** underwent further transformations under the mild reaction conditions at room temperature over a period of a few hours to as yet unidentified products.



1 **2** **3** **4**

When we examined the reaction of **1** or **5** in H_2O–Et_3N–MeCN for longer reaction times (5–48 h), we found that two new isomeric neutral compounds had been produced and eventually a third product. The latter was a carboxylic acid and had incorporated a molecule of water.

The three products **6**, **7** and **8** were separated by flash chromatography and their structures were elucidated by mass spectra, PMR, CMR, hetero COSY experiments, and in the case of **6** this was verified by X-ray diffraction analysis.[6a]

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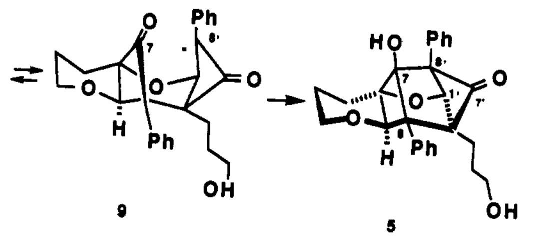
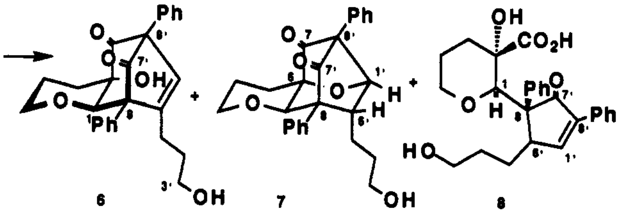


9 **5**

5 →



6 **7** **8**

Dimer **6** exhibited two carbonyl ketone signals at 201.4 and 201.3 ppm, IR at 1781 and 1705 cm^{-1}, and three sp^3 quaternary carbons at 77.1, 74.6, and 68.3 ppm. The proton NMR showed a vinylic triplet (J = 3.5 Hz) and two singlets at 5.06 (OH) and 4.56 (H-1) ppm. The characteristic two-hydrogen triplet of the opened side chain (H-3′) appeared at 3.47 ppm. Long-range hetereo COSY experiments showed a three-bond correlation from the vinylic proton to the two carbonyls (C-7, C-7′) as well as to C-8.[6b] The vinylic proton also had a two-bond correlation to C-8′. C-7 and C-7′ were correlated (three-bond) to H-1. X-ray data indicate intermolecular dimer formation via H-bonding between the two OH groups.

Dimer **7** had also two carbonyl signals at 201.5 and 198.9 ppm, IR at 1746 and 1694 cm^{-1}, and three sp^3 quaternary carbons at 80.8, 73.8, and 73.3 ppm. Its proton spectrum showed a doublet (J = 3.5 Hz) at 5.12 ppm for one of the oxymethine hydrogens (H-1′) and a dt (J = 3.5 and 4 Hz) at 2.66 ppm for the proton α to the side chain (H-6′). The other oxymethine proton (H-1) appeared as a singlet at

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[1] Stereochemistry 83. For paper 82 see Hassner, A.; Maurya, R.; Friedman, O.; Gottlieb, H. E.; Padwa, A.; Austin, D. *J. Org. Chem.* **1993**, *58*, 0000.

[2] Hassner, A.; Naidorf-Meir, S.; Gottlieb, H. E. *Tetrahedron Lett.* **1990**, *31*, 2181.

[3] (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Hoffmann, H. M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1.

[4] For some other examples see: (a) Hassner, A.; Fletcher, V. R. *Tetrahedron Lett.* **1970**, 1071. (b) Harding, K.; Trotter, J.; May, L. *J. Org. Chem.* **1977**, *42*, 2715. (c) Martin, P.; Greuter, H.; Bellus, D. *J. Am. Chem. Soc.* **1979**, *42*, 5853. (d) Hassner, A.; Dillon, J. *J. Org. Chem.* **1986**, *51*, 3315.

[5] Hassner, A.; Naidorf-Meir, S.; Gottlieb, H. E.; Goldberg, I. *J. Org. Chem.* **1992**, *57*, 2442.

[6] (a) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) Our numbering of carbons in dimers **4**–**8** is based on connecting two monomeric species **2** and **3** in which the non-hydroxylated monomeric species (derived from **2**) is assigned prime numbers.

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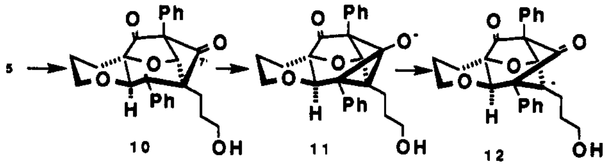
4.66 ppm. The trans assignment of H-6′ with respect to H-1′ is based on molecular mechanics conformational calculations. An α proton (cis to H-1′) was calculated to have a dihedral angle of 78° and $J_{H\text{-}6',H\text{-}1'}$ = 1.3 Hz, while a β (trans) hydrogen had an angle of 48° and $J_{H\text{-}6',H\text{-}1'}$ = 3.3 Hz. The latter is in agreement with the experimental value (3.5 Hz). Long-range hetero COSY showed a three-bond correlation between H-1 and the two carbonyls C-7 and C-7′.

Dimer **8** showed a low-field carbonyl at 210.8 ppm which is in agreement with a cyclopentenone system. The second carbonyl absorbed at 176.3 ppm indicating a carboxylic acid; the IR absorptions were at 1748 and 1702 cm^{-1}. The ^{13}C NMR spectrum showed two sp^3 quaternary carbons at δ 72.6 and 68.5 and a characteristic α,β-unsaturated olefinic system at 162.7 (CH) and 142.3 (C) ppm. In the proton spectrum this α,β-unsaturated system showed a low-field doublet at 7.94 (J = 3.5 Hz) and the oxymethine was characterized by a singlet at 3.73 ppm. The two-hydrogen triplet (H-3′ of the side chain) appeared at 3.68 ppm. Long-range hetero COSY exhibited a three-bond correlation between the vinylic proton H-1′ and both the ketone carbonyl C-7′ and C-8. The acid carbonyl C-7 can be correlated to H-1.

To account for formation of diketo olefin **6** from **5** it was necessary that the *tert*-alcohol at C-7 be transformed into a carbonyl group. The most logical transformation is therefore a retroaldol reaction of **5** with generation of enolate **9**. However we had shown[5] that it was precisely enolate **9** (generated from **4**) which due to proximity effects collapses to the strained product **5**, yet there is no other pathway that transforms **4** to **6**.

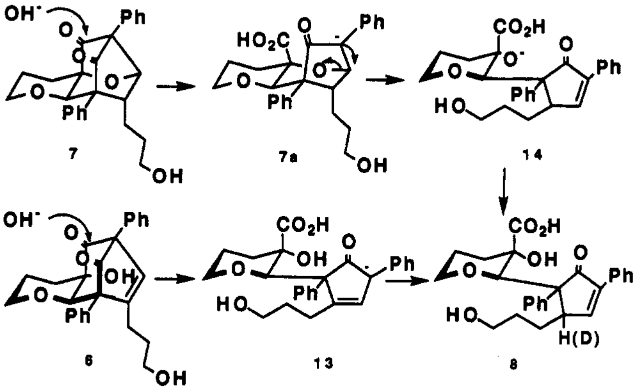
Furthermore, in order to produce **6** bonding between C-8 and C-7′ in the cage ketone **5** has to have occurred. A reasonable pathway for formation of **6** involves a rearrangement similar to a benzylic acid rearrangement involving opening of the strained cyclobutane ring (formation of anion **10**) with generation of a cyclopropanolate **11**. Cyclopropanols are known[7] to readily undergo ring opening to a β-keto carbanion, in this case with destruction of both the cyclopropane and the cyclobutane ring and generation of carbanion **12**. The latter can either get protonated to produce **7** or can undergo a β-elimination to afford olefin **6**.



At first glance the opening of the cyclobutanol ring in **5** to afford the obviously strained cyclopropanol **11** seems questionable, especially since it apparently involves generation of **10**, the *unusual reverse of addition of a benzylic carbanion to a ketone*. The following step (or occurring concertedly) is readdition of this carbanion to the cyclobutanone carbonyl. This process must be occurring in a reversible manner due to the proximity of the benzylic anion at C-8 to the carbonyl at C-7′. It was therefore of interest to compare the heats of formation of the cyclobutanol **5** and the cyclopropanol derived from **11**. This is legitimate since the two compounds are isomeric and contain the same kinds of functional groups. Molecular mechanics calculations[8] on these two compounds indicated the protonated form of **11** to be more stable than **5** by 68 kcal/mol. These calculations also showed that diketone **7** was more stable than protonated **11** by 34 kcal/mol.

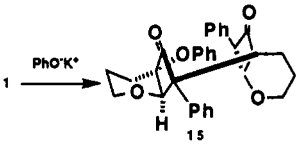
We showed that both **6** and **7** underwent further transformation under reaction conditions to afford carboxylic acid **8**. It was important to determine whether **7** was a precursor for **6** or whether an equilibrium between them existed. To this end olefin **7** was treated with TEA–D_2O in CD_3CN and the reaction was followed by NMR. Slow conversion to the acid **8** was observed without evidence of **6**. Conversely olefin **6** was converted to **8** without **7** being formed. However, carboxylic acid **8** resulting from **6** in D_2O was deuteriated at the allylic carbon C-6′ (vinyl proton a singlet at 7.90 ppm in CD_3CN–D_2O), whereas the product **8** generated from **7** in D_2O showed the vinylic proton signal as a doublet at 7.90 ppm.

These results indicate that **6** and **7** are not equilibrating under reaction conditions but are generated from **5** independently, one by protonation of **12** and the other by elimination of the alcoholate from **12**. Furthermore, olefin **6** undergoes attack by hydroxide ion on the β-diketone with formation of an allyl anion **13** that gets protonated (deuteriated) on carbon, whereas **7** undergoes a similar transformation but with formation of alcoholate **14**, without D-incorporation on carbon.



The ultimate product of these unusual transformations is the carboxylic acid **8** which according to molecular mechanics calculations[8] is indeed much more stable than either **5**, **11**, **6**, or **7** (49 kcal/mol more stable than **7** + H_2O).

As a further confirmation of the pathway leading from **4** via **9** to **5**, we found that reaction of chloro ketone **1** with PhOK (instead of H_2O–TEA) led exclusively to dimer **15** in high yield. This analog of **4** lacks the OH function necessary for further transformation to **5**, since no Michael addition to produce **9** is possible.



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(7) De Puy, C. H.; Dappen, G. M.; Eilers, K. L.; Klein, R. A. *J. Org. Chem.* **1964**, *29*, 2813.

(8) The molecular mechanics calculation were performed using "PC-MODEL" (Serena Software, Box 3076, Bloomington, IN 47402) running on an IBM RS/6000 workstation. The values obtained are only approximations.

Experimental Section

Reaction of 5 or of 1 with Water–TEA. Compound 5 (0.03 g) isolated as described,[5] was dissolved in 0.5 mL of CD_3CN–D_2O 9:1 and 1 equiv of TEA and allowed to stand at 20 °C. The reaction was followed by ^1H NMR. After a few min, 6 and 7 were observed in a ratio of 2:1; with time both 6 and 7 disappeared and acid 8 became the only product.

To 0.2 g (0.85 mmol) of chloro ketone 1 and 0.1 g of $LiClO_4$ in 10 mL of CH_3CN–H_2O: (9:1) was added 1.1 equiv of Et_3N. The mixture was stirred at 20 °C for 5 h, a few drops of 5% aqueous HCl were added, and the solvent was removed in vacuum. The residue was dissolved in EtOAc and the solution washed successively with water and saturated NaCl and dried ($MgSO_4$). Removal of the solvent left a mixture of dimers 6 and 7 that was chromatographed on silica gel (EtOAc–hexane 1:2 to 2:1) and each compound was crystallized separately. For isolation of the acid 8 the reaction of 1 was allowed to proceed for 48 h. The acid which precipitated was filtered and recrystallized.

11-Oxa-6,12-dioxo-3-(3′-hydroxypropyl)-2,5-diphenyl-7-hydroxytricyclo[5.4.0.1^{2,5}]-3-dodecene (6). Recrystallization from EtOAc–hexane gave white crystals (70 mg, 20% yield): mp 193 °C; ^1H NMR (acetone-d_6) δ 7.35 (m, 10H), 6.52 (t, J = 2 Hz, H-1′), 5.06 (s, OH), 4.56 (s, H-1), 3.81 (ddt, J = 11, 5, 2 Hz, H-3), 3.60 (td, J = 11, 3 Hz, H-3), 3.50 (OH), 3.47 (bt, 2H, J = 6.5 Hz, H-3), 2.66 (dtd, J = 12.5, 3.5, 2 Hz, H-4), 2.06 (dtd, J = 17.5, 7.5, 2 Hz, H-5′), 1.88 (dtd, J = 17.5, 7.5, 2 Hz, H-5′), 1.8–1.65 (m, 4H), 1.43 (m, H-4); ^{13}C NMR δ 201.4, 201.3 (C-7, C-7′), 152.7 (C-6′), 136.2, 133.5 (ipso's), 130.2, 130.1, 129.2, 128.7, 128.4, 128.2, 127.8, 124.1 (C-1′), 79.2 (C-1), 77.1 (C-8′), 74.6 (C-6), 68.3 (C-8), 67.2 (C-3), 62.2 (C-3′), 33.8 (C-5), 29.7, 28.0 (C-4′, C-5′), 23.9 (C-4); IR (KBr) 3541, 3300, 1781, 1705, 1498, 1446 cm^{-1}; MS CI (isobutane) m/z 419 (MH^+), 401 (M – H_2O), 391 (M – CO). Anal. Calcd for $C_{26}H_{26}O_5$: C, 74.62; H, 6.26. Found: C, 74.71; H, 6.40.

11,13-Dioxa-6,12-dioxo-3-(3′-hydroxypropyl)-2,5-diphenyltetracyclo[5.4.0.1^{2,5}.1^{4,7}]tridecane (7). Recrystallization from EtOAc–hexane gave 35 mg of white crystals (10% yield): mp 245–246 °C; ^1H NMR (acetone-d_6) 7.60 (m, 2H), 7.30 (m, 8H), 5.12 (d, J = 3.5 Hz, H-1′), 4.46 (s, H-1), 3.91 (ddd, J = 12, 5, 1 Hz, H-3), 3.77 (dt, J = 12, 3 Hz, H-3), 3.44 (t, 2H, J = 6 Hz, H-3′), 2.67 (dt, J = 10.5, 3.5 Hz, H-6′), 2.15 (m, 2H, H-5), 2.27 (m, H-4), 2.05 (m, H-5′), 1.77 (m, H-4), 1.63 (m, H-4′), 1.31 (m, H-4′), 1.24 (m, H-5′); ^{13}C NMR δ 201.5, 198.9 (C-7, C-7′), 136.3, 133.2 (ipso's), 129.6, 129.5, 129.2, 129.1, 128.9, 128.6, 81.6 (C-1′), 80.8 (C-6), 73.8 (C-1), 73.3 (C-8′), 69.0 (C-3), 63.2 (C-8), 62.5 (C-3′), 52.5 (C-6′), 30.4 (C-4′), 26.7 (C-5), 23.6 (C-4), 21.1 (C-5′); IR (KBr) 3498, 1748, 1694, 1498, 1447 cm^{-1}; MS CI (isobutane) m/z 419 (MH^+), 391 (M – CO). Anal. Calcd for $C_{26}H_{26}O_5$ + $^1/_2H_2O$: C, 73.41; H, 6.36. Found: C, 73.04; H, 6.29.

4-(3″-Hydroxypropyl)-2,5-diphenyl-4-(3′-hydroxy-3′-carboxy)tetrahydropyran-2′-yl)-2-cyclopenten-1-one (8). Recrystallization from acetonitrile afforded 90 mg of 8 (25% yield): mp 192 °C; ^1H NMR δ 7.94 (d, J = 3.5 Hz, H-1′), 7.67 (m, 2H), 7.38 (m, 5H), 7.18 (m, 3H), 4.14 (dd, J = 11, 5 Hz, H-3), 3.80 (s, H-1), 3.65 (t, J = 6 Hz, 2H, H-3′), 3.49 (ddd, J = 12.5, 11, 2.5 Hz, H-3), 3.55 (ddd, J = 10.5, 5, 3.5 Hz, H-6′), 2.41 (m, H-5′), 2.19 (m, H-4), 2.00 (m, H-5), 1.8–1.4 (m, 5H); ^{13}C NMR δ 210.8 (C-7′), 176.3 (C-7), 162.2 (C-1′), 142.3 (C-8′), 140.2, 132.5 (ipso's), 131.1, 129.7, 129.4, 128.6, 128.3, 128.2, 83.9 (C-1), 72.6 (C-6), 69.6 (C-3), 68.5 (C-8), 63.0 (C-3′), 55.1 (C-6′), 38.1 (C-5), 31.7 (C-4′), 31.2 (C-5′), 23.9 (C-4); IR (KBr) 3492, 1703, 1668, 1492 cm^{-1}; MS CI (isobutane) m/z 437 (MH^+), 419 (M – H_2O). Anal. Calcd for $C_{26}H_{28}O_6$ + $^1/_2H_2O$: C, 70.08; H, 6.56. Found: C, 70.18; H, 6.22.

1-Phenoxy-8-phenyl-8-(8′-phenyl-7′-oxo-2′-oxabicyclo[4.2.0]-octan-1′-yl)-5-oxa-*cis*-bicyclo[4.2.0]octan-7-one (15). Upon addition of a 0.2 g (0.85 mmol) of 1 to a solution of potassium phenoxide in THF a strong yellow color appeared, which disappeared after 5 min. The oil obtained after workup was purified by chromatography, eluent EtOAc–hexane 1:6. Recrystallization from CH_2Cl_2–petroleum ether gave 170 mg of white crystals in 83% yield: mp 183 °C; ^1H NMR ($CDCl_3$) δ 7.53 (m, 2H), 7.30 (m, 12H), 7.04 (m, 1H), 5.08 (d, J = 8 Hz, H-8′), 5.05 (d, J = 8 Hz, H-1′), 4.62 (d, J = 1.5 Hz, H-1), 3.76 (td, J = 12, 2 Hz, H-3′), 3.67 (ddd, J = 12, 4.5, 3 Hz, H-3′), 3.63 (ddd, J = 12, 10, 1 Hz, H-3), 3.43 (ddd, J = 12, 7, 5.5 Hz, H-3), 2.52 (bdt, J = 15.5, 3.5 Hz, H-5′), 2.15 (m, H-5), 1.88 (ddd, J = 15.5, 13.5, 5 Hz, H-5′), 1.5–1.3 (m, 3H), 1.14 (dm, J = 14 Hz, H-4′), 0.36 (qt, J = 13.5, 4 Hz, H-4′); ^{13}C NMR[9] δ 206.5 (C-7), 205.4 (C-7′), 154.4, 134.4, 133.3, 129.2, 128.4, 127.9, 127.2, 127.1, 123.1, 120.9, 89.2 (C-6), 75.5 (C-1), 70.9 (C-1′), 68.0 (C-6′), 62.8 (C-3), 60.5 (C-3′), 60.0 (C-8′), 23.2 (C-5′), 21.2 (C-5), 20.0 (C-4′), 17.3 (C-4); IR (KBr) 1770, 1580, 1490, 1440 cm^{-1}; MS CI (isobutane) m/z 496 (MH^+), 401 (MH – PhOH), 377 (MH – PhCHCO). Anal. Calcd for $C_{32}H_{30}O_5$: C, 77.71; H, 6.11. Found: C, 77.49; H, 6.01.

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(9) One of the quaternary carbons in 15 was not detectable presumably being hidden among other signals (quaternary carbons give notoriously weak signals).