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Solid-State Photodimerization of Cholest-4-en-3-one

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Crystalline cholest-4-en-3-one undergoes solid-state dimerization by UV radiation to give two ring A − ring A connected dimers. No dimerization occurs in solution. The first dimer, characterized by a cyclobutane ring, is formed by connection of C-2 and C-3 of a moiety with C-5′ and C-6′ of another moiety, respectively. The latter dimer has a six-membered ketal ring formed by connection of C-2 with C-5′ and of O, linked to C-3, with C-3′. The structures have been determined by spectroscopic means. X-ray analysis of title compound evidences the proximity of the axial H-2 of a molecule to the C-4′ of a molecule in the upper layer. The transfer of the hydrogen and the connection between C-2 and C-5′ might be the driving force of dimerization.

In a recent paper, we reported[1] that 16-dehydroprogesterone (**1**) underwent solid-state photodimerization to give dimer **2**, side-chain-ring D connected (Figure 1).

X-ray analysis of **1** revealed the proximity of the side chain of a molecule to the D ring of another one. The distances and the orientations between the C-21 methyl of a unit and the enone group of the other justified a bimolecular reaction consisting in the transfer of a hydrogen from the C-21 methyl to the olefinic C-16 carbon with subsequent connection of the C-21 radical onto the β-face of the C-17 one.

According to Hertel's postulate,[2] *the reaction in the solid state occurs with minimum amount of atomic or molecular movement*; dimerizations involving the enone group of the A ring were not observed. It is noteworthy that no connection between the D rings and/or the A rings was obtained in dispersed phase.

To investigate the influence of the topochemical factors on the dimerization of steroids possessing an enone function, we have now examined cholest-4-en-3-one (**3**), which has a head to head contact of the A rings of the molecules in the crystalline state as reported in the literature[3] where crystals from methanol solution are described. X-ray single-crystal experiments, performed on the starting crystalline commercial sample of cholest-4-en-3-one as well as on the one obtained by recrystallization from ethyl ether, both showed the maintenance of the same crystalline structure as reported in the literature (Figure 2). Powdered crystalline cholest-4-en-3-one (**3**) was irradiated with a Hanovia 450 W UV lamp for 4 h, and along with starting material, two dimers were isolated, which were attributed structures **4** and **6**.

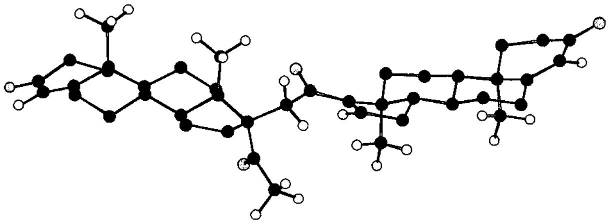
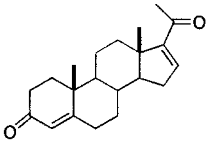


Figure 1. 3D structure of dimer **2**.



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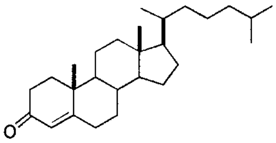

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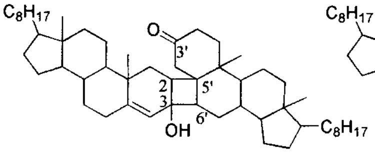

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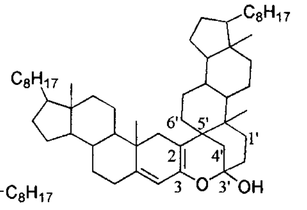

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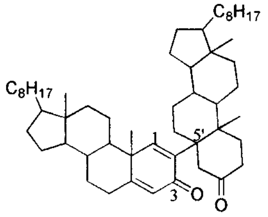

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10.1021/jo0015826 CCC: $20.00

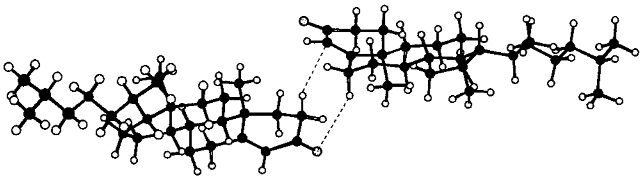

Figure 2. Proximity of the H-2β and O of a molecule to the C-4 and H-6α of a molecule of the upper layer in the crystalline lattice of **3**.

Dimer **4**, characterized by a cyclobutane ring, had molecular formula $C_{54}H_{88}O_2$ in agreement with its elemental analysis and the molecular peak at m/z 768 in the EIMS spectrum. The spectrum also showed a peak at m/z 750 due to the loss of water. In the IR spectrum, besides the carbonyl absorption at 1709 cm^{-1}, was present a hydroxyl absorption at 3594 cm^{-1}. The ^{13}C NMR spectrum showed only 39 signals, being integrated for two carbons the signals attributable to the C-20−C-27 side-chain carbons and those at δ 22.6 and 34.8, for three carbons the signal at δ 28.2 and for four carbons the signal at δ 56.1, in an inverse gated experiment. In the ^{1}H NMR spectrum were present an olefinic proton at δ 5.26, two methine protons as multiplets at δ 2.62 and 1.98, two methylene protons as AB doublets at δ 2.42 and 2. 47, four methyl singlets at δ 1.10 (× 2), 0.74, and 0.69, and six methyl doublets at δ 0.93 (× 2), 0.89 (× 2), and 0.87 (× 2) in addition to the remaining signals in the aliphatic region of the spectrum. In the HMBC spectrum the methylene protons at δ 2.42 and 2.47, linked to the carbon at δ 47.4 attributed to C-4′, were correlated to the C-3′ carbonyl carbon at δ 215.6, to the C-10′ carbon at δ 37.7, and to the C-6′ carbon at δ 46.6. The proton at δ 1.98, linked to the C-6′ carbon, had correlations with the carbinol C-3 carbon at δ 67.8, the olefinic C-4 carbon at δ 123.3, the C-5′ carbon at δ 39.5, and the C-10′ carbon. The H-2 proton at δ 2.62, linked to the carbon at δ 46.1, was correlated with the same carbons and had a further correlation with the C-10 carbon at δ 35.9. The H-1′ protons at δ 1.50 and 1.62 and the H-2′ protons at δ 2.16 gave cross-peaks with the C-3′ carbon, while the H-2′ and H-19′ protons at δ 1.10 were correlated to the C-10′ carbon. Finally, the H-1 protons at δ 1.88 and 1.45 were correlated to the C-5′, C-2, C-3, C-5 carbons at δ 148.7 and the C-19 carbon at δ 22.2 while the olefinic proton H-4 at δ 5.28 was correlated to the C-3 and C-10 carbons. In the ROESY spectrum, the H-2 and the H-6′ protons gave interactions with the coincident methyl protons at δ 1.10 which also interact with the H-4′ protons. While the NMR data defined the rough structure univocally, the steric connection between the moieties was ambiguous. The identical chemical shift of the H-19 methyls did not allow us to establish whether the H-2 and the H-6′ protons were cis and both oriented to give NOE with one of the H-19 methyls or whether they were trans and each one gave NOE with one of the methyls. X-ray analysis of cholest-4-en-3-one[3] showed that the 2β-proton of a molecule in a layer was about 2.6 Å from the C-4 of the close one in the upper layer. Hence, the first step of dimerization could be the hydrogen transfer with subsequent formation of the C-2−C-5′ bond to define a *cis*-decaline configuration (Figure 3). Such a dimer **5** has not been isolated, but the linkage should bring the H-6′ and the C-3 carbonyl oxygen, which in the reticule are separated by 3.1 Å, nearer. The second step could involve the transfer of the H-6′ hydrogen to the oxygen followed by the bond formation between C-6′ and C-3. This hypothesis suggested the trans configuration in the cyclobutane ring. Dimer **4** was crystallized from C_6H_6, and its crystal and molecular structure (Figure 4), determined by X-ray single-crystal analysis, confirmed the correctness of the hypothesis unambiguously.

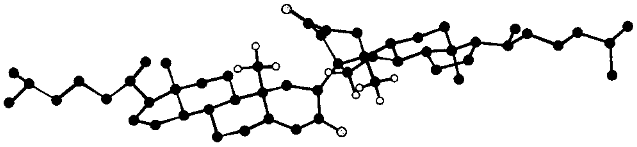

Figure 3. Dimer **5** by connection of C-2 and C-5′.

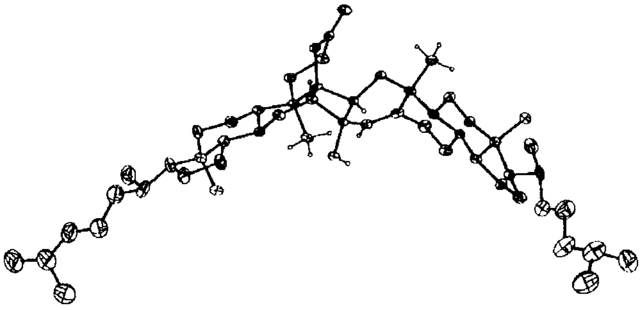

Figure 4. Molecular structure of dimer **4**.

Dimer **6** was characterized by a bond between the C-2 of a unit and C-5′ of a second one and a hemiketal grouping obtained by the C-3′ carbonyl and the oxygen of the enolic form of the C-3 carbonyl. The structure derived from the physical features of the compound. In the EIMS spectrum it had a molecular peak at m/z 768 and a composition in the elemental analysis that agreed with the molecular formula $C_{54}H_{88}O_2$. The ^{13}C NMR spectrum showed only 46 carbons, eight of them attributable to the C-20−C-27 carbons of the side chains. These were integrated for two carbons in an inverse gated experiment. In the low-field region of the spectrum, no carbonyl signal was detectable, and accordingly, the IR spectrum showed absorption at 3559 cm^{-1} of a hydroxyl function. DEPT experiments showed 10 methyls, 22 methylenes, and 13 methines, one of them at δ 115.8. The remaining signals may be attributed to six quaternary carbons, one of them at δ 98.6, and three vinylic carbons. The ^{1}H NMR spectrum showed the vinylic proton as a singlet at δ 5.41, two methylene protons at δ 2.52, as AB doublet, and 1.18, two methylene protons as AB doublets at δ 2.36 and 1.97, four methyl singlets at δ 0.65, 0.69, 0.92, and 0.99. All the remaining signals overlapped in the aliphatic region of the spectrum. Besides other correlations attributable to the remaining carbons and protons, the HMBC spectrum showed that the olefinic signal at δ 5.41, assigned to the H-4 proton, was heterocorrelated to the enolic C-2 carbon at δ 105.6 and to the C-10 carbon at δ 38.8. To the latter carbon the H-19 methyl protons at δ 0.99 and the H-1 methylene protons at δ 2.36 and 1.97 were also correlated. These protons gave further cross-peaks with the enolic C-2 carbon and with the quaternary carbon at δ 42.5, assigned to the C-5′ carbon. The C-5′ carbon was in turn correlated to the H-19′ methyl protons at δ 0.86 and to the H-4′ methylene protons at δ 2.52 and 1.18. Finally, these protons were also correlated to the enolic C-2 carbon and the hemiketal carbon at δ 98.6.

ROESY experiments furnished evidence of NOE interaction between the H-19 and H-19′ methyls as well

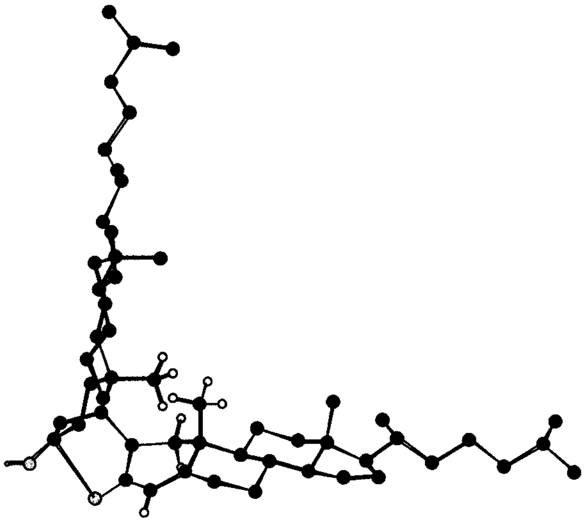

Figure 5. Minimum optimized structure of dimer **6**.

as their interaction with the H-1β proton at δ 2.36. These data require a *cis*-decalin junction in the hemiketal moiety.

A two-step process could also justify dimer **6** formation. After the connection of the monomers to give dimer **5,** there must be a rotation around the C-2−C-5′ bond to get near the carbonyl functions. The transfer of H-2α to the oxygen of the other unit, the formation of the double bond C-2−C-3, and the attack of the enolic oxygen to the C-3′ carbon affords dimer **6** (Figure 5).

Dimer **6** is not stable in dispersed phase and is converted into a further dimer, which has been attributed structure **7**. Such a dimer is characterized by a conjugated dienone in a moiety and a carbonyl function in the other one.

The presence of a molecular peak at *m/z* 766 in the EIMS spectrum of **7** and the elemental analysis were in agreement with the molecular formula $C_{54}H_{86}O_2$. Besides the coinciding signals of the C-17 and C-20−C-27 carbons of the two moieties, 36 signals were present in the ^{13}C NMR spectrum of **7**. These signals were identified by DEPT experiments as two carbonyl carbons at δ 208.5 and 187.7, four olefinic carbons at δ 166.6, 140.3, 157.2, and 124.9, the last two protonated, four methyls, 15 methylenes, six methines, and five quaternary carbons. The ^1H NMR spectrum showed two olefinic protons as singlets at δ 7.05 and 5.97, a methylene as AB doublets at δ 2.82 and 2.19, and four methyl singlets at δ 1.24, 0.84, 0.74, and 0.68, while all the remaining protons were overlapped in the aliphatic region.

According to the structure, in the HMBC spectrum the olefinic proton at δ 7.05, attributed to H-1, gave cross-peaks with the olefinic C-2 and C-5 carbons at δ 140.3 and 166.6, with the C-19 methyl carbon at δ 18.3 and the C-5′ quaternary carbon at δ 45.0. To this carbon the H-4′ methylene protons at δ 2.19 and 2.82 as well as the H-19′ methyl protons at δ 0.84 were also correlated. The H-19 methyl protons at δ 1.25 gave cross-peaks with the C-1 olefinic carbon at δ 157.2, the C-10 carbon at δ 45.9, and the C-5 carbon; the last two carbons are also related to the vinylic H-4 proton at δ 5.95. The H-4 proton along with the H-4′ protons gave cross-peaks with the C-2 vinylic carbon, and the last protons were also correlated to the C-3′ carbonyl carbon at δ 208.5 and the C-10′ carbon at δ 38.3.

The formation of **7** from **6** may be justified by the loss of hydrogen from the hemiketal hydroxyl group reinstating of the carbonyl function at C-3′. The subsequent restored carbonyl group at C-3 causes the shift of the double bond at C-1 with loss of hydrogen from this carbon. The molecular modeling of **7** is in agreement with the NOE data as in a ROESY spectrum where both the methyls H-19 and H-19′ interact with the olefinic proton H-1.

Reactions in the solid state occur with a minimum amount of molecular movement without strong distortion of the reactant lattice. This is the case of formation of dimer **4**, which has the reactive atoms at the right distances. The formation of dimer **6** requires a large conformational variation, which seems to conflict with the Hertel postulate. This theoretical difficulty can be released if dimerization is thought of as a superficial phenomenon as suggested by the following experimental evidence: (a) the yield of dimers increases with the degree of superficial extension; (b) comparison of X-ray single-crystal data of cholest-4-en-3-one, taken on the same crystal before and after the UV irradiation, showed no detectable variation in the cell parameters and in the characteristics of the diffraction peak profiles. The only remarkable variation was given by the slight but general decline of reflection intensities. These observations are in good agreement with a crystal degradation, which proceeds through a surface process.

Experimental Section

Irradiation of 3. Powdered **3** (200 mg), crystallized from Et_2O, was irradiated with a Hanovia 450 W lamp for 4 h to give a mixture of unreacted **3** (142 mg), **4** (18 mg), and **6** (14 mg) separated by flash chromatography on silica gel (hexane−Et_2O 19:1). A solution of **6** (10 mg) in $CHCl_3$ (2 mL) afforded **7** quantitatively after 48 h. **4**: EIMS *m/z* 768, 750, 446, 384; ^1H NMR ($CDCl_3$) (400 MHz) δ 5.26 (1H, s, H-4), 2.62 (1H, m, H-2), 2.47 (1H, d, $J = 12.4$ Hz, H-4′), 2.42 (1H, d, $J = 12.4$ Hz, H-4′), 1.98 (1H, m, H-2′), 1.10 (6H, s, H-19 and H-19′), 0.93 (6H, d, $J = 6.5$ Hz, H-21 and H-21′), 0.89 (6H, d, $J = 6.5$ Hz, H-26 and H-26′), 0.87 (6H, d, $J = 6.5$ Hz, H-27 and H-27′), 0.69 and 0.74 (2 × 3H, ss, H-18 and H-18′); ^{13}C NMR ($CDCl_3$) (100 MHz) δ 34.8 (C-1), 46.1 (C-2), 67.8 (C-3), 123.3 (C-4), 148.7 (C-5), 33.0 (C-6), 28.4 (C-7), 36.5 (C-8), 56.1 (C-9), 35.9 (C-10), 22.6 (C-11), 40.1 (C-12), 42.8 (C-13), 57.9 (C-14), 24.3 (C-15), 28.2 (C-16), 56.1 (C-17), 12.1 (C-18), 22.2 (C-19), 35.8 (C-20), 18.6 (C-21), 36.1 (C-22), 23.8 (C-23), 39.5 (C-24), 27.9 (C-25), 22.5 (C-26), 22.8 (C-27), 36.0 (C-1′), 34.8 (C-2′), 215.6 (C-3′), 47.4 (C-4′), 39.5 (C-5′), 46.6 (C-6′), 34.6 (C-7′), 33.1 (C-8′), 48.6 (C-9′), 37.7 (C-10′), 22.6 (C-11′), 39.9 (C-12′), 42.1 (C-13′), 56.1 (C-14′), 24.2 (C-15′), 28.2 (C-16′), 56.1 (C-17′), 12.1 (C-18′), 20.9 (C-19′), 35.8 (C-20′), 18.6 (C-21′), 36.1 (C-22′), 23.8 (C-23′), 39.5 (C-24′), 27.9 (C-25′), 22.5 (C-26′), 22.8 (C-27′); IR ν_{max} ($CHCl_3$) 3594, 1709 cm^{-1}; UV (λ_{max}, ϵ) 241, 934. Anal. Calcd for $C_{54}H_{88}O_2$: C, 84.30; H, 11.53. Found: C, 84.21; H, 11.44.

6 had: EIMS *m/z* 768, 753, 446, 384; ^1H NMR ($CDCl_3$) δ 5.41 (1H, s, H-4), 2.52 (1H, d, $J = 15.4$ Hz, H-4′), 2.36 (1H, d, $J = 14.8$ Hz, H-1), 1.97 (1H, d, $J = 14.8$ Hz, H-1), 1.18 (1H, d, $J = 15.4$ Hz, H-4′), 0.99 (3H, s, H-19), 0.92 (3H, s, H-19′), 0.93 (6H, d, $J = 6.5$ Hz, H-21 and H-21′), 0.89 (6H, d, $J = 6.5$ Hz, H-26 and H-26′), 0.87 (6H, d, $J = 6.5$ Hz, H-27 and H-27′), 0.69 (3H, s, H-18), 0.65 (3H, s, H-18′); ^{13}C NMR ($CDCl_3$) δ 38.5 (C-1), 105.6 (C-2), 145.3 (C-3), 115.9 (C-4), 146.8 (C-5), 31.4 (C-6), 28.2 (C-7), 41.7 (C-8), 54.8 (C-9), 38.8 (C-10), 21.8 (C-11), 40.2 (C-12), 41.0 (C-13), 56.0 (C-14), 24.2 (C-15), 28.3 (C-16), 56.3 (C-17), 11.9 (C-18), 19.0 (C-19), 35.8 (C-20), 18.7 (C-21), 36.1 (C-22), 23.8 (C-23), 39.5 (C-24), 28.0 (C-25), 22.6 (C-26), 22.8 (C-27), 30.4 (C-1′), 30.6 (C-2′), 98.6 (C-3′), 38.7 (C-4′), 42.5 (C-5′), 34.6 (C-6′), 26.7 (C-7′), 35.4 (C-8′), 56.7 (C-9′), 42.5 (C-10′), 21.5 (C-11′), 40.0 (C-12′), 41.5 (C-13′), 56.2 (C-14′), 24.3 (C-

15′), 28.2 (C-16′), 56.2 (C-17′), 12.0 (C-18′), 17.9 (C-19′), 35.8 (C-20′), 18.7 (C-21′), 36.1 (C-22′), 23.8 (C-23′), 39.5 (C-24′), 28.0 (C-25′), 22.6 (C-26′), 22.8 (C-27′); IR ν_{max} ($CHCl_3$) 3559, 1660 cm^{-1}; UV (λ_{max}, ϵ) 285, 600. Anal. Calcd for $C_{54}H_{88}O_2$: C, 84.30; H, 11.53. Found: C, 84.39; H, 11.47.

7: EIMS *m/z* 766, 751, 446, 420; ^1H NMR ($CDCl_3$) δ 7.05 (1H, s, H-1), 5.97 (1H, s, H-4), 2.82 (1H, d, $J = 16.0$ Hz, H-4′), 2.19 (1H, d, $J = 16.0$ Hz, H-4′), 1.24 (3H, s, H-19), 0.92 (6H, d, $J = 6.5$ Hz, H-21 and H-21′), 0.89 (6H, d, $J = 6.5$ Hz, H-26 and H-26′), 0.88 (6H, d, $J = 6.5$ Hz, H-27 and H-27′), 0.84 (3H, s, H-19′), 0.74 (3H, s, H-18), 0.68 (3H, s, H-18′); ^{13}C NMR ($CDCl_3$) δ 157.2 (C-1), 140.3 (C-2), 187.7 (C-3), 124.9 (C-4), 166.6 (C-5), 32.2 (C-6), 31.7 (C-7), 35.4 (C-8), 52.6 (C-9), 45.9 (C-10), 23.0 (C-11), 31.7 (C-12), 42.4 (C-13), 55.4 (C-14), 24.4 (C-15), 28.1 (C-16), 56.1 (C-17), 11.9 (C-18), 18.3 (C-19), 35.7 (C-20), 18.6 (C-21), 36.1(C-22), 23.8 (C-23), 39.5 (C-24), 28.0 (C-25), 22.6 (C-26), 22.8 (C-27), 32.0 (C-1′), 35.9 (C-2′), 208.5 (C-3′), 43.9 (C-4′), 45.0 (C-5′), 33.5 (C-6′), 27.3 (C-7′), 34.6 (C-8′), 55.7 (C-9′), 38.3 (C-10′), 21.5 (C-11′), 40.0 (C-12′), 42.6 (C-13′), 56.5 (C-14′), 24.2 (C-15′), 28.3 (C-16′), 56.1 (C-17′), 12.0 (C-18′), 19.1 (C-19′), 35.7 (C-20′), 18.6 (C-21′), 36.1 (C-22′), 23.8 (C-23′), 39.5 (C-24′), 28.0 (C-25′), 22.6 (C-26′), 22.8 (C-27′); IR ν_{max} ($CHCl_3$) 1685, 1658, 1622 cm^{-1}; UV (λ_{max}, ϵ) 248, 13,600. Anal. Calcd for $C_{54}H_{86}O_2$: C, 84.52; H, 11.30. Found: C, 84.39; H, 11.41.

X-ray Analysis of Dimer 4. Compound **4** was recrystallized from C_6H_6. The unit cell parameters were obtained by a least-squares fitting of the setting values of 25 strong reflections in the θ range $27 \leq \theta \geq 30°$. The X-ray data were collected on an automatic diffractometer using the ω/θ scan technique. Three monitoring reflections, measured every 300, showed insignificant intensity fluctuations. The intensities were corrected for Lorentz and polarization factors whereas absorption was neglected. The structure was solved by direct methods.[4] The full-matrix least-squares refinement minimized the quantity $w^{-1} = [\sigma^2(F_o) + (0.02F_o)^2 + 1.5\ ]$ where σ is derived from counting statistics. As the uncyclized fragments of dimeric molecule were found affected by a remarkable disorder, a best model of these parts was fitted into the electron density map and refined as constrained fragments. All other non-hydrogen atoms were refined anisotropically. The H atoms, generated at their expected positions taking into account the indications of the difference Fourier map for the methyl and hydroxyl groups, were included but not refined in the final structure factors calculations. The final refinement cycles included a secondary extinction parameter that converged to a value of $8.0(2) \times 10^{-8}$. The junction between the two moieties of dimer is stiffened by an intramolecular H-bond which links the hydroxyl and the keto oxygen atoms.

All crystallographic calculations were performed by using the Enraf-Nonius (SDP) set of programs.[5]

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Supporting Information Available: ^1H NMR, ^{13}C NMR, COSY, DEPT, ROESY, HMQC, HMBC, and crystallographic data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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