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Synthesis and Characterization of Atropisomers Arising from 1,3-Cyclohexanediones by Intermolecular Tandem-Michael/Michael Additions

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Intermolecular tandem-Michael/Michael addition reactions of alkyne acceptors and CH-acidic compounds such as 1,3-cyclohexanedione (**2a**) and dimedone (**2b**) under L-proline catalysis furnished four new products **1a–d** with C_2 axial chirality.

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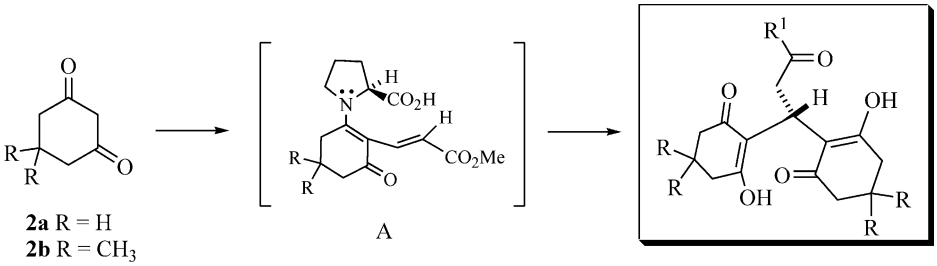
Introduction

The double Michael reaction is a useful synthetic strategy in organic synthesis that allows the atom-economic construction of complex carbon frameworks through the formation of two bonds in one step, for example, the *trans*-decalins and *trans*-hydrindanes.[1,2] This reaction has also been applied to the construction of the carbon skeletons of different natural products such as (±)-cedranediol,[3] (–)-epibatidine,[4] and substituted piperidinones.[5] Recently, tandem-1,4-additions mediated by phosphanes or aryl thiolates were reported by Murphy and co-workers.[6]

Perhaps the most familiar example was provided by the pioneering work of Stork and Tomasz on the concise synthesis of griseofulvin which they obtained from an active methylene compound and a cross-conjugated enynone.[7] However, intermolecular C_2-symmetric tandem-Michael/Michael products **1a–d** (Scheme 1) derived from the reactions of β-dicarbonyl compounds **2** with alkynes are unknown and might prove to be valuable structures for asymmetric synthesis.



1a R = H, R^1 = OCH_3
1b R = H, R^1 = CH_3
1c R = CH_3, R^1 = OCH_3
1d R = CH_3, R^1 = CH_3

Scheme 1. Preparation of **1** by a tandem-Michael/Michael process. Reagents and conditions: ≡–C(O)R^1 (R^1 = CH_3, OCH_3), DMSO, cat. L-proline, room temp.

In connection with our study on the synthesis of polycyclic compounds of biological interest[8] we now report the preparation, structural analysis, and properties of new atropisomeric products **1**. These compounds were obtained from the chiral enaminones of 1,3-cyclohexanediones **2**[9]

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with activated π systems like Michael acceptors (methyl propiolate and butynone). It is interesting to recall here that, as in compounds **1**, a 1,3-dione motif is found in cordypyridones A and B, two natural products that are atropisomers of each other which exhibit potent in vitro antimalarial activity.[10]

Results and Discussion

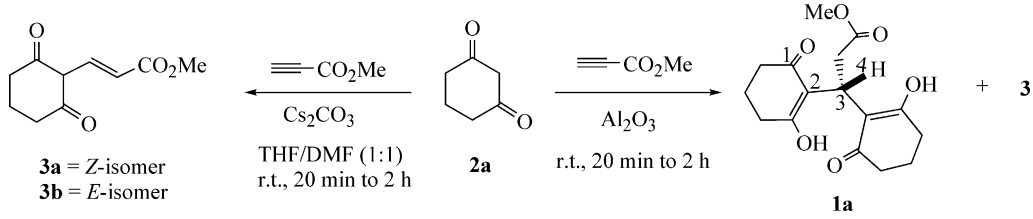
At first we found that the treatment of **2a** with methyl propiolate and Cs_2CO_3[11] in THF/DMF (1:1) at room temperature gave rise to the monoadducts **3**, with the *E* isomer being predominant (18:1, *E*:*Z* ratio), after isolation by careful column chromatography (Scheme 2). After that, based on our previous work on solid-support addition,[8b] we used methyl propiolate on alumina at room temperature. Thus, under magnetic stirring or sonication, an interesting tandem conjugate addition took place to give the chiral product **1a** together with the minor adduct **3** (Scheme 2).

After several attempts the reaction of **2a** with methyl propiolate on a solid support gave the best results under sonication with a 1:1.1 ratio of **2a**/alkyne; the pure products **1a** and **3** were obtained in 25 and 6% yields, respectively. These results encouraged us to carry out the amine-catalyzed addition of **2a** to methyl propiolate using L-proline in DMSO at room temperature under magnetic stirring;[12] compound **1a** was generated in 65% yield as the sole isolated product. We rationalized that **1a** was formed by means of an intermolecular double Michael reaction via the sp^2 acceptor **A** generated in situ, which then undergoes another addition by a second molecule of the enaminone donor (Scheme 3). The nucleophilic attack on **A** was assumed to take place on the less hindered face of the double bond (*Si* face), *anti* to the carboxy substituent borne by the proline moiety.

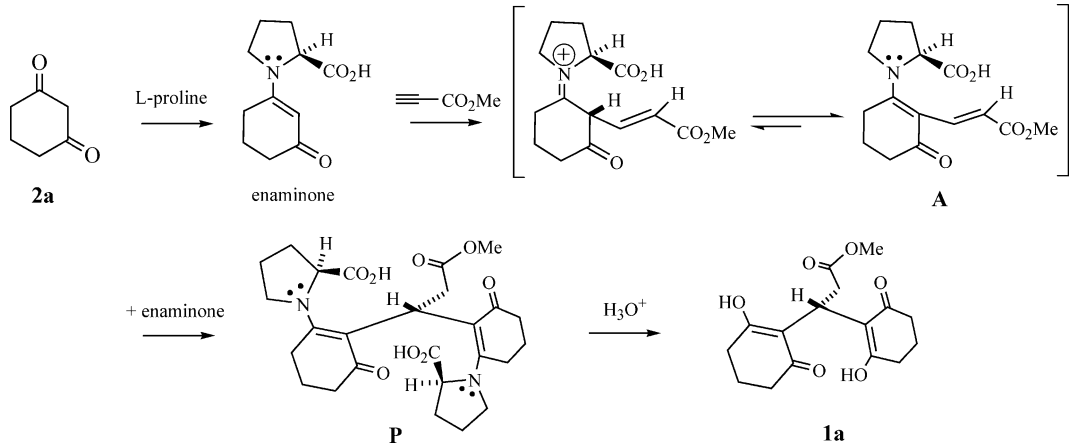
In the same manner as the alumina method (Scheme 2), it is evident that there is competition between two possible reactions when a new Michael acceptor is generated and it reacts with a second diketone (or the corresponding enaminone) instead of methyl propiolate, directing the reaction towards the preferential formation of **1a** whenever 1–10 mmol of dione were used.

This hypothesis was supported by measurement of the product concentration **P** versus reaction time by the periodic spectral lecture NMR method. Thus, equivalent amounts of **2a** and methyl propiolate in [D_6]DMSO under catalysis with L-proline were placed in a NMR tube and shaken at room temperature (Figure 1).

In Figure 1 (top) it is possible to see that after 13 d (approx. 350 h) of reaction, recording two sets of spectroscopic data a day, monitoring of the CH and OCH_3 signals by ^{1}H NMR indicated a progressive conversion of the starting material into **P** without detection of the monoadduct **A**. A time course for the reaction is illustrated in Figure 1 (bottom) with the stack plot of ^{1}H NMR spectra recorded during the experiment. The product formation was determined by integration of the signals arising from the methine proton and the methoxy group at δ = 4.50 and 3.70 ppm, respectively. We also verified the proposed mechanism with the preparation and isolation of the enaminone resulting from the reaction of **2a** with L-proline,[13] showing that chiral induction involved a covalent bond and that this enaminone then reacted with methyl propiolate to afford **P**.



Scheme 2. Michael addition of **2a** to methyl propiolate in solution and on a solid support.



Scheme 3. Mechanism for the Michael/Michael addition of **2a**.

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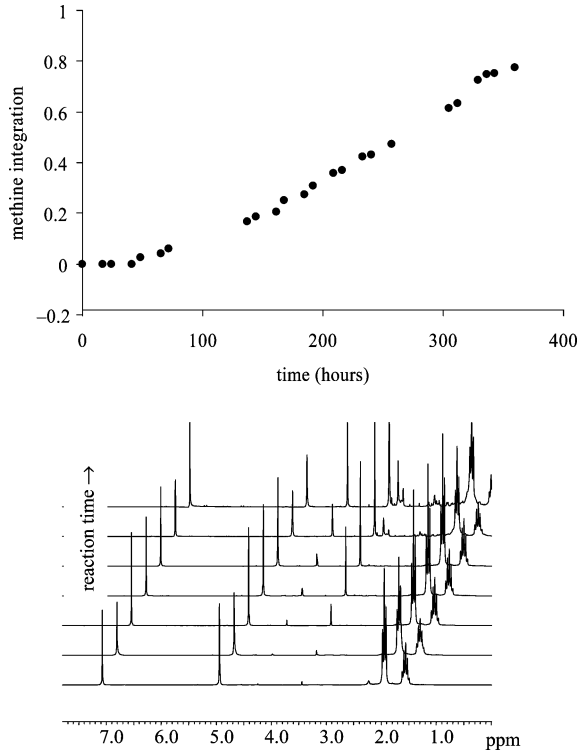

Figure 1. Top: concentration of **P**, as determined by methine signal integration, vs. reaction time when tandem-Michael addition of **2a** was carried out by catalysis with L-proline. Bottom: ^{1}H NMR spectral stack plot of the reaction **2a**→**P** recorded by the periodic spectral lecture ^{1}H NMR method. The behavior of the OCH_3 (δ = 3.70 ppm) and CH (δ = 4.50 ppm) groups of **P** during the reaction was considered in the calculation of the degree of conversion.

With regard to the molecular structure, **1a** has restricted rotation around the $C_2(sp^2)$–$C_3(sp^3)$ bond (Scheme 2, arbitrary numbering) giving rise to conformational chirality, that is, atropisomerism,[14] with the rings forced into different planes with all groups being maintained in a tetrahedral arrangement in space with a C_2 axis. Also, taking into account the structural portion of the vinylogous acid (conjugate enol form), associated keto/enol tautomerism might be considered.[15,16] The structure of **1a** was supported by IR spectroscopy, coupling constant analysis of the ^{1}H and ^{13}C NMR spectra, 2D NMR spectroscopy (HQBC and HMBC), selective irradiation, and mass spectrometry experiments. In the infrared spectra the absorption band at 1589 cm^{-1} and a hydroxy absorption band are strong evidence for the presence of the enol form of the 1,3-dicarbonyl compounds. In the ^{1}H NMR spectrum recorded in [D]chloroform the most significant signals, which fall at δ = 4.50 and 3.04 ppm, were assigned to the methine 3-H and the α-ester proton resonances, respectively, with an equivalent coupling constant ^3J = 7.5 Hz. Selective irradiation of the doublet centered at δ = 3.04 ppm removed its coupling effect with the neighboring 3-H to give a singlet. In addition, the presence of the signal at δ = 12 ppm in the ^{1}H NMR spectrum together with the signals of the sp^2 carbons at 196.9, 172.2, and 114.2 ppm in the ^{13}C NMR spectra are consistent with the vinylogous acid portion. Some of the absorption peaks observed as duplicate signals in the ^{1}H NMR spectrum indicated a slow tautomeric interconversion at room temperature (Figure 2). Hence, variable-temperature NMR experiments carried out at temperatures ranging from 37 to 52 °C showed us that the equilibrium is so fast that the protons labeled with a and a′ with of the enol moieties are magnetically equivalent, whereas at lower temperatures (from 7 to –23 °C) the experiment revealed two sets of signals for Ha, Ha′, and CH_2, confirming the two rings have different magnetic environments. The enolic hydroxy proton peak at δ = 13 ppm, observed as a singlet at 7 °C, was shifted upfield and became two singlets centered at 13 and 12.5 ppm at –43 °C.

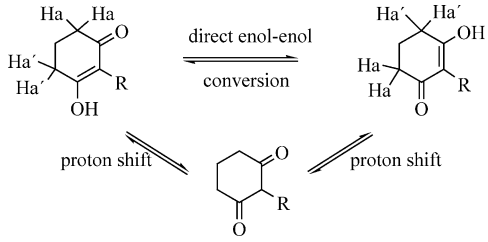

Figure 2. Tautomerization process for the dicarbonyl compounds **1**.

To gain more structural information we performed molecular modeling studies on **1a**. The molecule was minimized by using the B3LYP/6-31+G(d,p) basis set, as described in the Exp. Section, and the result is shown in Figure 3 (bottom). As can be seen, it shows a 3D arrangement with an out-of-plane *anti* orientation of the vinylogous groups in both rings with an angle between them of –21°. It also exhibits additional stabilization through two intramolecular hydrogen bonds. This structure has been superimposed with the recently published crystal structure of 2,2′-methylenebis(3-hydroxy-5,5-dimethylcyclohex-2-en-1-one), which shows a similar arrangement of the bicyclic system.[17] Further evidence confirming the presence of a hydrogen bond is one broad and diffuse band at 3400 cm^{-1} in the infrared spectra, which has been assigned to the presence of an enolic hydroxy group involved in intramolecular hydrogen-bonding.[18] Rotation around C1–C2–C3–H4 (cf. Scheme 2) was calculated to have a rotational barrier of 40 kcal mol^{-1} for the conformer with the lowest energy. The energy value determined for the conformer with the highest energy (at a dihedral angle of 210 °) is a consequence of the strong steric hindrance between the carbonyl of the carboxylate group and the carbonyl of one of the rings.

All this evidence demonstrates the high stability of the minimum energy conformation. Also the high value found for the energy barrier permitted speculation about the presence of atropisomerism. In addition, these compounds show low optical rotations $[\alpha]_D$ which are also temperature-dependent.

The CD spectrum of **1a** revealed the existence of one optically active species with a positive multiple Cotton effect near 245 and 300 nm which correlates with the π→π* UV absorption of an α,β-unsaturated ketone.[19]

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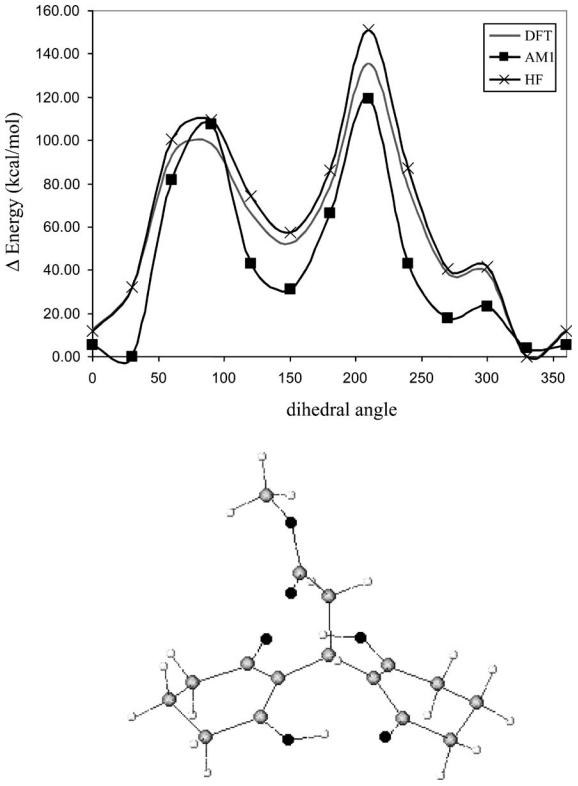

Figure 3. Top: superimposed conformational energy diagram for **1a**: single point (AM1), Hartree–Fock (HF), and (density functional theory, DFT). Bottom: representation of the global minimum energy conformation of **1a**.

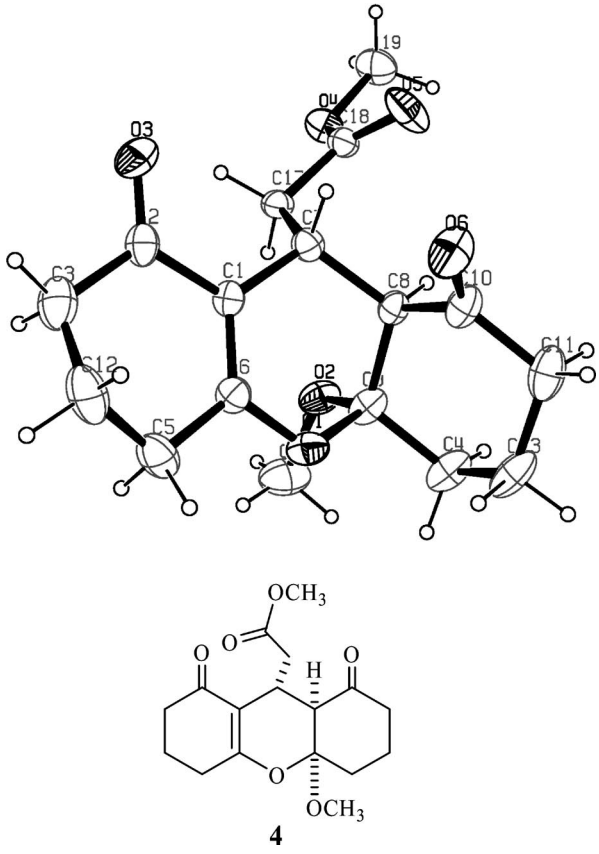

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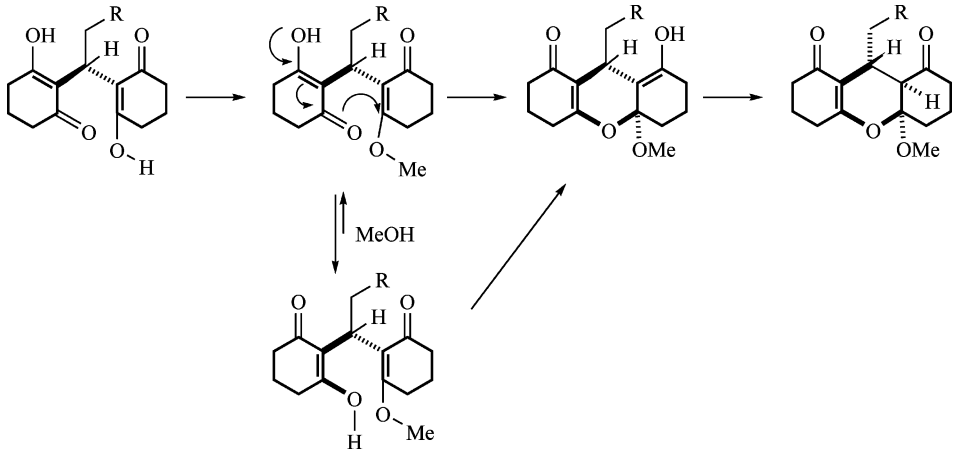
Figure 4. Top: ORTEP plot showing the structure of the derivative **4** in the solid state obtained from a single-crystal X-ray analysis. Bottom: structure of **4**.

An attempt at X-ray analysis of **1** failed due to the low quality of the crystals obtained. Also, several alkylsilyloxy derivatives of **1** were prepared, but they were isolated as oils at room temperature. Finally, the reaction of **1a** with diazomethane and careful crystallization from ethanol gave the methylated derivative **4** which was submitted to single-crystal X-ray diffraction analysis.[20] An ORTEP drawing of this structure, corresponding to a substituted decahydroxanthene, is shown in Figure 4.

The formation of tricyclic derivative **4** is consistent with a diazomethane-mediated vinylogous esterification followed by a 1,4-addition to the newly formed ester portion originating a new ring. The formation of this six-membered ring (center ring of the xanthene skeleton) imposes new confor-



Scheme 4. Reaction mechanism for the transformation **1**→**4** with diazomethane in methanol.

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mational restraints causing the separation of the other carbonyl and enolic hydroxy groups. As a consequence, the remaining hydrogen bond is broken and the isolated enol group tautomerizes to the more stable ketone with the proton disposed to form a *cis* junction (Scheme 4).[21]

Thus, the structural characterization of derivative **4** lends support to the proposed structure of parent compound **1a**. The presence of optical activity in derivative **4** indicated to us that the transformation **1a**→**4** occurred through a selective mode of attack on one of the enolic forms thus preventing racemization.

Compounds **1b**–**d** exhibit similar behavior to that of **1a**; in the case of **1b**, the side-chain permits the formation of a hemiacetal.

Conclusions

In summary, we have developed a new route to the formation of sp^2–sp^3 atropisomers by means of Michael addition reaction between 1,3-diones and alkynes. By catalysis with L-proline, an unusual intermolecular tandem process was observed. Compounds **1a**–**d** possess tautomerism as a result of axial chirality around the C2–C3 bond (cf. Scheme 2). We envision that this will allow us to design new related compounds and to explore their applications in asymmetric syntheses.

Experimental Section

General: Optical rotations: Jasco Model DIP 1000 polarimeter. Melting points (uncorrected) were measured in open capillary tubes with an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra: NMR Bruker AC-200E and Bruker Avance 300 MHz spectrometers in $CDCl_3$. FTIR spectra: Shimadzu, Prestige 21 Model. HPLCL Hewlett–Packard Series 1100 Model, LiChroCART® 250–4 LiChrospher®100 RP-18 and ChiraDex® columns. A two-solvent gradient elution was performed at a flow rate of 0.7–1 mL min^{-1}. The solvent compositions used were (A) water/methanol and (B) water/acetonitrile (v/v). All samples were microfiltered before injection. All solvents were HPLC grade. CD data were recorded in MeOH (0.59×10^{-6} M), absorbance 0.631 (λ_{max} = 261 nm) on a Jasco Model J-810 spectropolarimeter at the Department of Chemistry, University of Córdoba. HRMS: recorded at the UCR Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside, USA. Ab initio calculations were performed with Gaussian 98.[22] Rotational energy barrier calculation: a full conformational search was performed on **1a** by using the conformation search algorithm as is implemented in Hyperchem® 6.0.[23] The minimum was optimized by density functional calculations using Gaussian 98[22] and the B3LYP/6-31+G(d,p) basis set and the nature of the minimum was confirmed by vibrational analysis. The energy barrier was calculated by single-point calculations every 30° over the dihedral angle C1–C2–C3–H4 (Scheme 2).

General Procedure for the Synthesis of 1: A solution of L-proline (3.4 mg, 1.5 mol-%), the corresponding alkyne (2 mmol) in DMSO (1.8 mL), and 1,3-cyclohexanedione **2** (2 mmol) was stirred at room temperature for 13 d. EtOAc (2 mL) and a saturated NH_4Cl solution (4 mL) were added and the aqueous layer was extracted with EtOAc (4 × 3 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue on silica gel (hexane/EtOAc) gave 62–68% of pure crystalline **1**.

1-(3-Oxocyclohex-1-enyl)pyrrolidine-2-carboxylic Acid (Enaminone): A solution of **2a** (112 mg, 1 mmol) and L-proline (115 mg, 1 mmol) in benzene (5 mL) was heated at reflux with azeotropic removal of water using a Dean–Stark apparatus for 5 h. The solvent was then evaporated and the residue distilled under vacuum to give enaminone as a pale-yellow oil in quantitative yield after purification by flash chromatography (EtOAc/EtOH, 50:50). $[\alpha]_D^{22}$ = +102.6 (*c* = 2.5, Cl_3CH), IR (film): $\tilde{\nu}$ = 3416 [–C(O)–*OH*], 2951, 1718 [–*C(O)*–OH], 1580 (enaminone), 1542, 1534 (C=C), 1437, 1336, 1198, 1145, 668 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 10.1 (br. s, 1 H, acid H), 5.37 (s, 1 H, 2′-H), 4.26 (t, *J* = 4.4 Hz, 1 H, 2-H), 3.74 (m, 1 H, 5-H), 3.54 (m, 1 H, 5-H), 2.53 (m, 2 H, 6′-H), 2.31 (t, *J* = 6.2 Hz, 2 H, 4′-H), 2.25 (m, 2 H, 3-H), 1.99 (m, 4 H, 4-H and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.3 (C=O, enaminone), 173.1 (C=O acid), 166.8 (=C–N), 98.1 (C-2′), 61.9 (C-2), 49.2 (C-5), 34.1 (C-4′), 30.1 (C-6′), 27.8 (C-3), 23.5 (C-4), 21.5 (C-5′) ppm.

Compound P: To a solution of the enaminone (523 mg, 2.5 mmol) in DMSO (1.8 mL) was added methyl propiolate (0.24 mL, 3 mmol). The reaction mixture was stirred at room temperature for 13 d. Water and EtOAc were added. The aqueous layer was extracted with EtOAc (5 × 3 mL) and the organic layers were dried, filtered, and concentrated. By flash chromatography compound **P** was isolated in 75% yield as an oil. $[\alpha]_D^{25}$ = –3.30 (*c* = 0.72, Cl_3CH). IR (film): $\tilde{\nu}$ = 3400 [–C(O)–*OH*], 2945, 1736 [–*C(O)*–OMe], 1727 [–*C(O)*–OH], 1654, 1609 (enaminone), 1436, 1398, 1172, 998 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.83 (br. s, 2 H, acid H), 4.46 (t, *J* = 7.6 Hz, 1 H), 3.86 (m, 2 H, 2-H), 3.70 (m, 4 H, 5-H), 3.67 (s, 3 H, –OCH_3), 3.03 (d, *J* = 7.6 Hz, 2 H, C*H*$_2$CO$_2$Me), 2.51–2.15 (complex signal, 12 H), 2.00–1.88 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.3 (C=O enaminone), 181.5 (–COOH), 172.0 (C=O ester), 168.7 (=C–N), 116.9 (=*C*–C=O), 52.7 (*C*H–COOH), 51.6 (–OCH_3), 48.2 (CH_2–N), 36.9 (*C*H$_2$–C=O), 35.8 [*C*H$_2$–C(O)–Me], 34.6 (*C*H$_2$–C=C–C=O), 28.4 (*C*H$_2$–CH–N), 26.2 (–*C*H–CH$_2$–CO$_2$Me), 22.2 (*C*H$_2$–CH$_2$–N), 20.4 (*C*H$_2$–CH$_2$–C=O) ppm. MS (EI): *m*/*z* (%) = 502 (10) $[M]^+$, 322 (25), 248 (23), 234 (27), 204 (82), 162 (93), 146 (50), 73 (100).

Methyl 3,3-Bis(2-hydroxy-6-oxocyclohex-1-enyl)propionate (1a): Flash chromatography of the residue on silica gel (hexane/EtOAc, 60:40) furnished white crystals; m.p. 126–127 °C. $[\alpha]_D^{22}$ = –3.84 (*c* = 0.1, Cl_3CH). CD: $[\Phi]_{243}$ = 3300 (*c* = 0.06 mM, MeOH). IR (film): $\tilde{\nu}$ = 3400 (OH), 2954, 2360, 1731 (C=O, ester), 1589 (C=C enol of diketone), 1435, 1387, 1197, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.00 (br. s, 1 H), 4.50 (t, *J* = 7.3 Hz, 1 H), 3.62 (s, 3 H, OCH_3), 3.04 (d, *J* = 7.5 Hz, 2 H), 2.40 (m, 8 H), 1.88 (br. s, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 196.9 (C=O ketone), 172.2* (=C–OH), 165.8* (C=O ester), 114.2 (*C*=C–OH), 51.0 (OCH_3), 36.9 (CH_2), 36.8 (CH_2–C=O), 27.0 (CH_2–COH), 23.6 (CH), 20.3 (CH_2–*C*H$_2$–CH_2) ppm. Signals marked with * may be interchanged. HRMS: calcd. for $C_{16}H_{20}O_6$ 308.1260: found 309.1327 $[MH]^+$.

Methyl 2-[(4aR,9R,9aS)-4a-methoxy-1,8-dioxo-2,3,4,4a,5,6,7,8,-9,9a-decahydro-1*H*-xanthen-9-yl]acetate (4): Compound **1a** (30 mg, 0.1 mmol) was dissolved in methanol (1 mL) and cooled to 0 °C. A solution of diazomethane in ethyl ether was added and the mixture stirred for 1 h as the temperature gradually raised to 25 °C. The solvent was removed in vacuo to afford **4** as white solid, recrystallized from EtOH in quantitative yield; m.p. 129–130 °C. $[\alpha]_D^{26}$ = –1.35 (*c* = 0.94, Cl_3CH). IR (film): $\tilde{\nu}$ = 2947, 2850, 1725 (C=O ester), 1718 (C=O ketone), 1653 (α,β-unsaturated ketone), 1628, 1549, 1437, 1385, 1165, 1097, 1078, 950, 663 cm^{-1}. ^{1}H NMR [$(CD_3)_2$-

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CO]: δ = 3.75 (m, 1 H), 3.65 (s, 3 H, –OCH_3), 3.30 (s, 3 H, –OCH_3), 3.08 (m, 1 H), 2.83 (m, 2 H), 2.55–2.20 (m, 8 H), 2.10–1.80 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 204.7 (C=O), 197.3 (α,β-unsaturated C=O), 173.7 (C=O ester), 166.8 (=*C*–O–C), 113.6 (*C*=C–O–C), 103.3 (O–*C*–OMe), 54.1 and 51.3 (–OCH_3), 49.0 (*C*H–C=O), 40.2 (*C*H_2–C–OMe), 37.1 (*C*H_2–C=O), 35.5 (*C*H_2–C=O), 31.7 (*C*H_2–CO_2Me), 28.2 (*C*H_2–C–O–C), 20.7 and 20.1 (*C*$H_2$$CH_2$-C=O) ppm.

2,2′-(3-Oxobutane-1,1-diyl)bis(3-hydroxycyclohex-2-enone) (1b): Flash chromatography of residue on silica gel (hexane/EtOAc, 70:30) gave white and pure crystals; m.p. 123–124 °C. $[\alpha]_D^{29}$ = –8.4 (*c* = 0.1, Cl_3CH). IR (film): $\tilde{\nu}$ = 3390 (OH), 2944, 2360, 1720 (C=O ketone), 1618 (C=O enol of diketone), 1592 (C=C enol of diketone), 1435, 1389, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.7 (br. s, 1 H), 4.56 (t, *J* = 7.1 Hz, 1 H), 3.20 (d, *J* = 7.1 Hz, 2 H), 2.43–2.15 (m, 12 H), 2.10 [s, 3 H, C(O)CH_3], 1.75–1.50 (m, 8 H), 1.40 [s, 3 H, C(OH)C*H*$_3$] ppm. ^{13}C NMR ($CDCl_3$): δ = 206.4 (C=O ketone, side-chain), 196.8 (C=O ketone, hemiketal), 191.8 and 190.7 (C=O, keto-enol), 166.7 (=*C*–OC, hemiketal), 117.4 (*C*=C–OH), 117.3 (*C*=C–O–C, hemiketal), 99.8 [q, *C*(OH)CH_3], 43.8 [*C*H_2–C(O)-CH_3], 39.0 [*C*H_2–C(OH)CH_3], 37.8 (CH, hemiketal), 37.1 and 36.5 (*C*H_2–C=O, ketone), 34.3 (*C*H_2C=O, hemiketal), 33.2 and 32.5 (*C*H_2–C=O keto-enol), 29.8 [C(O)*C*H_3], 27.8 (*C*H_2–O–C, hemiketal), 24.2 [C(OH)*C*H_3], 24.0 (CH), 20.6, 19.7, and 18.3 (CH_2–*C*H_2–CH_2) ppm. HRMS: calcd. for $C_{16}H_{20}O_5$ 292.1311; found 293.1324 $[MH]^+$.

Methyl 3,3-Bis(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propionate (1c): Flash chromatography of the residue on silica gel (hexane/EtOAc, 75:25) gave white crystals; m.p. 82–83 °C. $[\alpha]_D^{32}$ = –0.12 (*c* = 1.1, Cl_3CH). IR (film): $\tilde{\nu}$ = 3390, 2957, 2871, 1738 (C=O ester), 1596 (C=C enol of diketone), 1472, 1388, and 1369 (*gem*-dimethyl), 1168 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.40 (br. s, 1 H), 4.51 (t, *J* = 7.7 Hz, 1 H), 3.59 (s, 3 H, OCH_3), 3.05 (d, *J* = 7.7 Hz, 2 H), 2.26 and 2.25 [s, 8 H, –C*H*$_2$C(O), keto-enol], 1.02 (br. s, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 190.1 and 189.5 (keto-enol), 172.5 (C=O ester), 115.7 (*C*=C–OH), 51.6 (OCH_3), 46.8 and 46.1 (*C*H_2–C=O, keto-enol), 34.3 (*C*H_2–CO_2Me), 31.0 [*C*$(CH_3)_2$], 29.8 (*C*H), 25.8 (*C*H_3) ppm. HRMS: calcd. for $C_{20}H_{28}O_6$ 364.1886; found 365.1971$[MH]^+$.

2,2′-(3-Oxobutane-1,1-diyl)bis(3-hydroxy-5,5-dimethylcyclohex-2-enone) (1d): Flash chromatography of residue on silica gel (hexane/EtOAc, 70:30) gave white crystals; m.p. 169–170 °C. $[\alpha]_D^{31}$ = +0.78 (*c* = 0.35, Cl_3CH). IR (film): $\tilde{\nu}$ = 3412 (OH), 2960, 1714 (C=O, ketone), 1597 (C=C enol of diketone), 1471, 1382, and 1373 (*gem*-dimethyl), 1140 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 12.40 (br. s, 1 H), 4.57 (t, *J* = 7.3 Hz, 1 H), 3.22 (d, *J* = 7.3 Hz, 2 H), 2.28 [br. s, 8 H, CH_2C(O), keto-enol], 2.11 [s, 3 H, C(O)CH_3], 1.05 and 1.04 (s, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 206.3 (C=O ketone), 190.1 and 189.4 (C=O, keto-enol), 116.1 (*C*=C–OH), 46.8 and 46.1 (*C*H_2–C=O, keto-enol), 43.4 [*C*H_2–C(O)CH_3], 31.1[*C*$(CH_3)_2$], 30.0 (*C*H), 26.4 [C(O)*C*H_3], 24.0 [C(*C*$H_3)_2$] ppm. HRMS: calcd. for $C_{20}H_{28}O_5$ 348.1937; found 349.2017 $[MH]^+$.

Methyl (*Z*)- and (*E*)-3-(2,6-Dioxocyclohexyl)acrylate (3a and 3b): Solid Cs_2CO_3 (869 mg, 2.6 mmol) was added to a solution of **2a** (224 mg, 2 mmol) in THF/DMF (1:1, 10 mL) and the mixture was stirred at room temperature for 20 min. After that methyl propiolate (0.18 mL, 2 mmol) was slowly added dropwise and the mixture was allowed to stand at room temperature for 1 h. The reaction mixture was concentrated, the residue was dissolved in Et_2O (15 mL), and extracted with brine solution (3 × 15 mL). The organic layers were washed with water (3 × 5 mL), dried with anhydrous Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography (hexane/EtOAc, 70:30) gave isomers *E* (235.3 mg, 60%) and *Z* (12 mg, 3%) in a ratio of 18:1, respectively, as oils.

3a: IR (film): $\tilde{\nu}$ = 3456 (=C–OH), 2926, 1745 (ester), 1681 (unsaturated C=O), 1631(C=C), 1564, 1412, 1306, 1058, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.83 (d, *J* = 9.9 Hz, 1 H), 6.23 (d, *J* = 9.5 Hz, 1 H), 3.75 (OCH_3), 2.87–1.50 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 191.6 and 190.9 (C=O, keto-enol), 172.5 (ester), 139.7 (*C*=CH–CO_2Me), 116.8 (C=*C*H–CO_2Me), 51.4 (OCH_3), 36.4 (CH), 34.6, 33.3, 32.6, 28.1, 26.1, 19.8 ppm.

3b: IR (film): $\tilde{\nu}$ = 3419 (=C–OH), 2922, 1732 (ester), 1635 (unsaturated C=O), 1620(C=C), 1450, 1379, 935 cm^{-1}. ^{1}H NMR (D_2O): δ = 7.79 (d, *J* = 14.6 Hz, 1 H), 6.57 (d, *J* = 15.7 Hz, 1 H), 3.62 (s, 3 H, OCH_3), 3.10–1.70 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 192.0 and 190.7 (C=O, keto-enol), 173.0 (ester), 139.5 (*C*=CH–CO_2Me), 115.6 (=*C*–CO_2Me), 51.8 (OCH_3), 36.6 (CH), 34.8, 33.0, 32.8, 28.4, 26.8, 19.1 ppm.

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