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# A Simple and Efficient Route to 1,4-Diketones from Squaric Acid

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**Abstract:** Squaric acid derivatives react with organolithium compounds at room temperature to afford with excellent yields after hydrolysis, symmetrical and unsymmetrically substituted oxygenated 1,4-diketones bearing alkyl, aryl or heteroaryl groups at the carbonyl positions. In the case of aromatic or heteroaromatic ketones the enol tautomers are also obtained.

1,4-Diketones are important synthetic intermediates as precursors for the synthesis of heterocyclic[1] and carbocyclic[2] compounds. For this reason, several synthetic strategies have been developed in the last few years for their preparation. The most important approaches include the formation of one[3] or two[4] C-C bonds of the $C_4$ framework or are based on the ring opening of furans[5] or the interconversion of functional groups[6] in linear 1,4-disubstituted precursors. However, no general method for the synthesis of 1,4-diketones has been reported by using the C-C bond cleavage of a suitable 1,2-dicarbonyl four membered ring as the key step of the preparation.[7] The thermally activated ring opening of cyclobutenes is a well established process leading to butadienes. Cyclobutene-1,2-diols undergo ring opening at high temperature in the presence of acids or amines to afford furans or pyrroles.[8] The presence of electron-donating substituents on the ring lowers significantly the temperature required for the cyclobutene ring opening.[9] On the other hand, pinacol dianions undergo radical C-C bond cleavage to give ketones[10] by oxidation in air. On these grounds, we thought that squaric acid derivatives appear to be attractive and convenient commercially available starting materials for the preparation of 1,4-difunctional compounds upon $C_1$-$C_2$ bond cleavage (see Figure 1).

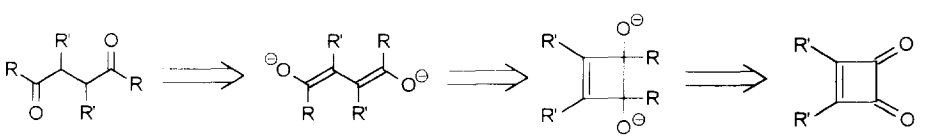
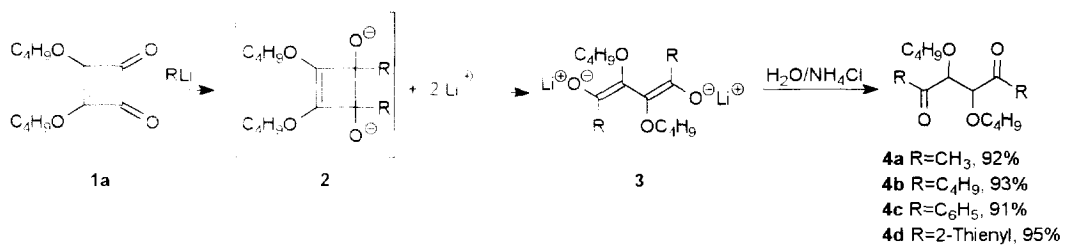


**FIGURE 1**

## RESULTS AND DISCUSSION

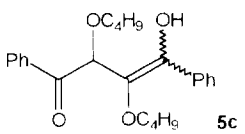
Now we wish to report a new very efficient method for the synthesis of disubstituted 1,4-diketones **4** based on simple squaric acid chemistry. The reaction of dibutyl squarate (**1a**) with organolithium compounds at room temperature followed by acid hydrolysis yielded the corresponding symmetrical 1,4-diketones (**4**) with excellent yields (see Scheme 1). Only the double 1,2-addition of the organolithium derivative[11] to the carbonyl groups was observed to occur. The organolithium reagent was employed in excess to avoid the



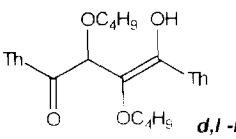

**SCHEME 1**

formation of products resulting from monoaddition of the organometallic reagent to the carbonyl groups. In all cases the resulting pinacol dianion **2** undergoes at room temperature a clean process of ring opening with isomerization of the double bond to give a dienolate **3** which yields the corresponding diketone **4** upon acid hydrolysis. Diketones **4a** and **4b** were obtained as the expected mixtures of *meso*- and *d,l*-diastereomers in *ca.* 1:1 molar ratio. Each diastereomer could be isolated by HPLC. The determination of the relative stereochemistry of the isomers was carried out by $^1$H-NMR upon addition of Eu(hfc)$_3$ which allowed to observe in the case of the racemic mixtures *d,l*-**4a** and *d,l*-**4b** the splitting of the signal corresponding to the methine group into two singlets with the same intensity. The $^1$H-NMR spectra of these compounds show characteristic patterns for the methylene -OCH$_2$- groups which appear as two double triplets centered at *ca.* δ 3.2 and 3.5 ppm in the case of the *meso*-diastereomers and an unresolved multiplet centered at *ca.* δ 3.5 ppm in the *d,l*- mixtures. Aromatic diketone **4c** was obtained as a mixture of diastereomers and the *E*- and *Z*-monoenol tautomers **5c** as determined by the NMR spectrum (DCCl$_3$). In this case the enolization takes place with great ease most probably due to the conjugation of the double bond with the aromatic ring and, for this reason, the tautomers could not be isolated separately. To ascertain the identity of the tautomers the pyrrole **6c** was prepared by heating the mixture with aniline in chloroform and acetic acid. By contrast, it is noteworthy that the reaction of 2-thienyllithium with **1a** occurred in a diastereospecific fashion giving rise exclusively to the ketone *meso*-**4d** free from its *d,l*-diastereomers. The stereochemistry of this compound could be easily assigned by the characteristic pattern of the -OCH$_2$- groups in the $^1$H-NMR spectrum which is very similar to that observed for the same groups in compounds *meso*-**4a** and *meso*-**4b**. The enolization of ketone **4d** which

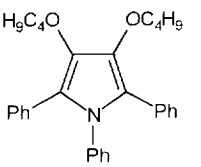
is also favored by the conjugation of the thienyl ring with the C=C double bond, gave selectively a single monoenol tautomer *E*-**5d**. Its stereochemistry was unequivocally determined by the observation of a $^1H$-$^1H$



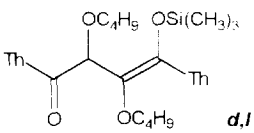

**5c**



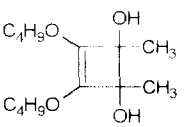

***d,l* -*E*-5d**



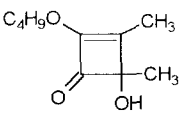

**6c**




***d,l* -*E*-7d**




**8a**




**9a**

**CHART**

nOe between the $(CH_3)Si$- and the methine group in the O-trimethylsilyl derivative **7d**. To account for the different behavior towards the enolization of ketones **4c** and **4d**, it should be considered that in the lithium enolate *E*-**5d** $Li^+$ the sulfur atom in the thienyl ketone can coordinate with the lithium alkoxide (see Figure 2). This type of stabilization is not posible in the case of the *Z*-stereomer. Of course, in the case of monoenols **5c** this effect is also absent due to the substitution of a phenyl group for the thienyl ring. In addition, the suggested coordination of lithium in *E*-**5d** $Li^+$ also accounts for the diastereospecific course of the protonation of this enolate which affords exclusively compound *meso*-**4d** due to the steric hindrance to the protonation by the *syn*-diastereoface relative to the coordinated butoxy group (see Figure 2).

To check the effect of the temperature, the addition reaction ($R=CH_3$) was also tried at -78 °C. Under these conditions, a *ca.* 2:1 mixture of the cyclic diol **8a** and 1,4-diketones **4a** was obtained when the hydrolysis was performed also at this low temperature. Diol **8a** could be characterized in the crude reaction mixture after solvent removal but was unstable towards the acids and could not be purified by column chromatography. Under these conditions **8a** was cleanly transformed into the hydroxyketone **9a**. By contrast, when the reaction mixture was hydrolyzed at room temperature only the 1,4-diketones **4a** were obtained.

Reactions were also successfully carried out to address the synthesis of unsymmetrically substituted 1,4-diketones. Differentially 3,4-disubstituted-3-cyclobutene-1,2-diones are easily obtained according the Moore[12] and Liebeskind[13] methodology. In this way, 3-(1-methylethoxy)-4-phenylcyclobut-3-ene-1,2-dione (**10**) was prepared from diisopropyl squarate (**1b**)[13a] and then treated with three equivalents of butyllithium under our standard conditions to yield the unsymmetrical 1,4-diketones *erythro*-**4e** and *threo*-**4e** (Scheme 2). The structural assignment of these stereomers was done by NMR considering the effect of the phenyl group on the chemical shifts of the neighboring groups. The phenyl ring in the most stable conformation[14] of compound

*erythro*-**4e** is *gauche* to a butylketone group and *anti* to the *iso*-propoxy group. Consequently, one of the carbonyl carbon atoms is shielded by 4.2 ppm by the aromatic ring, while the methyl groups in the *iso*-propyl ring are nearly equivalent and give a single signal in the $^1$H-NMR spectrum. Conversely, in the most stable conformation[14] of compound *threo*-**4e** the phenyl group is *gauche* to the *iso*-propoxy group giving rise to the splitting of the signal due to the methyl groups into two doublets centered at δ 0.70 and 1.07 ppm respectively. Furthermore, the methine $OCH(CH_3)_2$ signal in the *threo*-**4e** diketone is shielded by 0.3 ppm relative to the *erythro* isomer due to the proximity of the phenyl ring (see Figure 2).

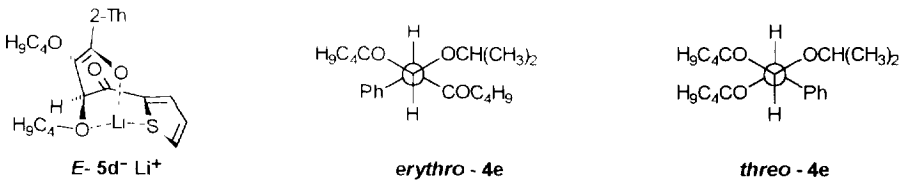
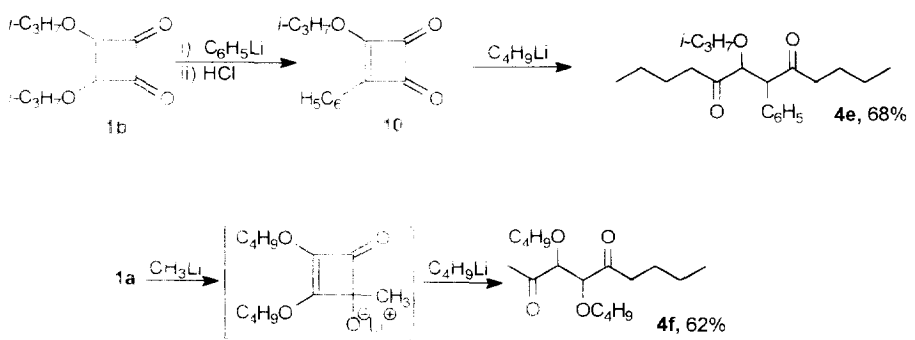



**FIGURE 2**

In order to obtain other type of unsymmetrical diketones we performed the successive addition of two different organolithium compounds to **1a**. One equivalent of methyllithium was added to **1a** at -78 °C and the mixture was stirred for thirty minutes. After reaching room temperature, two equivalents of *n*-butyllithium were added to yield after usual work-up the unsymmetrical diketones *erythro*- and *threo*-**4f** (Scheme 2). Based on their similar structures, the stereochemical assignment of these compounds was easily done by comparison of their $^1$H-NMR spectra and those of compounds **4a** and **4b**. The methylene -$OCH_2$- corresponding to the butoxy groups shows the same pattern for *erythro*-**4f** and *meso*-**4a** or **4b** while the spectrum of *threo*-**4f** is similar to that of *d,l*-**4a** and **4b**.




**SCHEME 2**

From the above results we can conclude that the addition of organolithium compounds to squaric acid derivatives appears to be a general useful methodology for the synthesis of symmetrical and unsymmetrically substituted oxygenated 1,4-diketones bearing alkyl, aryl or heteroaryl groups at the carbonyl positions. The recent development of short and practical synthetic approaches to substituted cyclobutenediones from squaric acid[12,13,15] allows prediction that the methodology described herein should be easily extended to the synthesis of 1,4-diketones with a great variety of substituents on $C_2$-$C_3$.

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## EXPERIMENTAL SECTION

*General Aspects.* $^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker AC200 and a Bruker AC250 spectrometers. IR spectra were run on a Perkin Elmer 843 spectrometer. High resolution mass spectra were conducted on a VG AUTOSPEC instrument. HPLC was performed with a Waters Millipore 510 chromatograph equipped with a Waters Differential Refractometer R401 and a column μPorasil (7.8 x 300 mm) or a reverse-phase column μBondapak C18 (7.8 x 300 mm).

Diethyl ether was dried with sodium and was distilled prior to use. Di-*n*-butyl squarate, (**1a**) di-*iso*-propyl squarate (**1b**), and the organolithium reagents used were purchased from Aldrich Chemical Co. 3-(1-Methylethoxy)-4-phenylcyclobut-3-ene-1,2-dione (**10**) was prepared according the literature method.[13a]

*General Procedure for the Preparation of Symmetrical 1,4-Diketones* **4a-d**. A solution of di-n-butyl squarate (**1a**) (2.0 mmol) in dry ether (5 mL) under argon was added to a ether solution (15 mL) of the corresponding organolithium compound (6.0 mmol) at room temperature. After 15 min (2 hours for methyllithium addition) the reaction mixture was hydrolyzed with saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ethyl acetate, the combined organic layers dried with sodium sulfate and the solvents removed in vacuum. The oily residue was purified by column chromatography on silica gel using hexane:ethyl acetate (95:5) as eluent yielding the corresponding mixture of diastereomers **4**.

*3,4-Dibutoxy-2,5-hexanedione* (**4a**). 474 mg of a 1:1 mixture of *meso*-**4a** and *d,l*-**4a** were obtained (92% yield) after chromatography. Separation of the diastereomers was performed by HPLC with a reverse-phase

column μBondapak and water:methanol (3:7) as eluent. Determination of the relative stereochemistry for each ketone was carried out by recording the $^1$H-NMR spectra of 0.3 mmol of the corresponding compound in $CDCl_3$ (0.4 ml) in the presence of 0.2 equiv. of Eu(hfc)$_3$. The first compound eluted was ***meso*-4a**: oil; IR (neat) $\nu_{max}$ : 2956, 2928, 2869, 1717, 1457, 1350, 1095 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 0.90 (t, $J$ = 7.3 Hz, 6H), 1.30-1.42 (m, 4H), 1.50-1.65 (m, 4H), 2.28 (s, 6H), 3.29 (dt, $J$ = 9.2, 6.5 Hz, 2H), 3.55 (dt, $J$ = 9.2, 6.5 Hz, 2H), 3.99 (s, 2H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 13.76 (q), 19.15 (t), 27.45 (q), 31.58 (t), 72.42 (t), 86.48 (d), 210.26 (s). HRMS (FAB) Calcd for $C_{14}H_{27}O_4$: 259.1909. Found: 259.1908. **(*d,l*)-4a**: oil; IR (neat) $\nu_{max}$ : 2956, 2924, 2869, 1717, 1458, 1351, 1109 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 0.93 (t, $J$ = 7.3 Hz, 6H), 1.30-1.48 (m, 4H), 1.52-1.65 (m, 4H), 2.22 (s, 6H), 3.55 (m, 4H), 3.98 (s, 2H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 13.82 (q), 19.26 (t), 27.36 (q), 31.82 (t), 71.47 (t), 86.53 (d), 209.42 (s). HRMS (FAB) Calcd for $C_{14}H_{27}O_4$: 259.1909. Found: 259.1909.

*6,7-Dibutoxy-5,8-dodecanedione* (**4b**). 629 mg of a 1:1 mixture of *meso*-**4b** and *d,l*-**4b** were obtained (93% yield) after column chromatographic purification. Separation of the diastereomers was performed by HPLC with a μPorasil column and hexane as eluent. Determination of the relative stereochemistry for each diketone was carried out by recording the $^1$H-NMR spectra of 0.3 mmol of the corresponding compound in $CDCl_3$ (0.4 ml) in the presence of 0.2 equiv. of Eu(hfc)$_3$. The first compound eluted was **(*d,l*)-4b**: oil; IR (neat) $\nu_{max}$ : 2955, 2930, 2869, 1716, 1463, 1339, 1115 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 0.90 (t, $J$ = 7.3 Hz, 6H), 0.91 (t, $J$ = 7.3 Hz, 6H), 1.26-1.47 (m, 8H), 1.49-1.63 (m, 8H), 2.55 (m, 4H), 3.52 (m, 4H), 4.00 (s, 2H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 13.80 (q), 13.91 (q), 19.22 (t), 22.30 (t), 24.97 (t) 31.84 (t), 39.35 (t), 71.38 (t), 86.30 (d), 210.96 (s). HRMS (FAB) Calcd for $C_{20}H_{39}O_4$: 343.2848. Found: 343.2843. ***meso*-4b**: oil; IR (neat) $\nu_{max}$ : 2955, 2930, 2869, 1715, 1463, 1327, 1096 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 0.89 (t, $J$ = 7.3 Hz, 6H), 0.92 (t, $J$ = 7.3 Hz, 6H), 1.23-1.44 (m, 8H), 1.48-1.63 (m, 8H), 2.51 (dt, $J$ = 18.4, 7.3 Hz, 2H), 2.73 (dt, $J$ = 18.4, 7.3 Hz, 2H), 3.27 (dt, $J$ = 9.3, 6.5 Hz, 2H), 3.53 (dt, $J$ = 9.3, 6.5 Hz, 2H), 4.02 (s, 2H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 13.78 (q), 13.91 (q), 19.13 (t), 22.30 (t), 24.86 (t) 31.66 (t), 39.40 (t), 72.54 (t), 86.56 (d), 211.98 (s). HRMS (CI) Calcd for $C_{20}H_{39}O_4$: 343.2848. Found: 343.2843.

*2,3-Dibutoxy-1,4-diphenyl-1,4-butanedione* (**4c**). 695 mg of a yellow oil were obtained after column chromatographic purification (91% yield). NMR spectra revealed that *meso*-**4c** and (*d,l*)- **4c** were present in equilibrium with their monoenol tautomers **5c** and the pure compounds could not be isolated. $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ (C=O) 198.98 (s), 198.45 (s), 197.99 (s), and 197.61(s); (CH) 84.66 (d), 81.40 (d), 73.92 (d) and 72.19 (d). HRMS (EI) Calcd for $C_{24}H_{30}O_4$: 382.2144. Found: 382.2132.

*2,3-Dibutoxy-1,4-bis(2-thienyl)-1,4-butanedione* (**4d**). Following the above described general procedure 758 mg of a mixture of *meso*-**4d** and its monoenol tautomer (*E*-**5d**) were obtained after column chromatographic purification (95% yield). Pure samples of these products were obtained by preparative TLC in silicagel with a mixture 9:1 hexane: ethyl acetate as eluent. ***meso*-4d**: oil; IR (neat) $\nu_{max}$ : 3096, 2954, 2929, 2867, 1647, 1580, 1511, 1409, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.69 (t, *J* = 7.2 Hz, 6H), 1.09 (sext, *J* = 7.2 Hz, 4H), 1.21-1.47 (m, 4H), 3.23 (dt, *J* = 9.2, 6.7 Hz, 2H), 3.56 (dt, *J* = 9.2, 6.1 Hz, 2H), 4.62 (s, 2H), 7.12 (dd, *J* = 4.7, 4.0 Hz, 2H), 7.68 (dd, *J* = 4.7, 1.0 Hz, 2H), 8.16 (dd, *J* = 4.0, 1.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.62 (q), 18.84 (t), 31.34 (t), 72.02 (t), 86.36 (d), 127.84 (d), 134.72 (d), 134.80 (d), 141.26 (s) 191.99 (s). HRMS (EI) Calcd for $C_{20}H_{26}O_4S_2$: 394.1272 Found: 394.1276. *E*-**5d**: oil; IR (neat) $\nu_{max}$ : 3444, 3090, 2955, 2930, 2869, 1654, 1576, 1512, 1412, 1101, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.89 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.3 Hz, 3H), 1.35 (sext, *J* = 7.3 Hz, 2H), 1.50 (sext, *J* = 7.3 Hz, 2H), 1.63-1.85 (m, 4H), 3.83 (m, 3H), 4.02 (dt, *J* = 9.2, 6.7 Hz, 1H), 4.25 (brs, 1H, $D_2O$-ex), 5.81 (s, 1H), 7.03 (dd, *J* = 4.9, 3.8 Hz, 1H), 7.11 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.29 (dd, *J* = 3.8, 1.2 Hz, 1H); 7.32 (dd, *J* = 5.0, 1.2 Hz, 1H); 7.68 (dd, *J* = 4.9, 1.1 Hz, 1H); 7.98 (dd, *J* = 3.8, 1.1 Hz, 1H); $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.79 (q), 13.93 (q), 18.96 (t), 19.24 (t), 31.92 (t), 31.98 (t), 72.20 (t), 72.26 (d), 74.18 (t), 126.00 (d), 126.42 (d), 126.66 (d), 128.56 (d), 133.59 (d), 134.71 (d), 135.47 (s), 139.50 (s), 142.44 (s), 143.89 (s) 190.82 (s). HRMS (EI) Calcd for $C_{20}H_{26}O_4S_2$: 394.1272 Found: 394.1272

*6-(1-Methylethoxy)-7-phenyl-5,8-dodecanedione* (**4e**). Dione **10**[13a] was used instead of di-n-butyl squarate (**1a**) as starting material and the preparation followed the above-described procedure for symmetrical diketones, yielding 451 mg of a 1:1.5 mixture of the *erythro*-**4e** and *threo*-**4e** (68% yield). Separation of the diastereomers was performed by preparative TLC (alumina, hexane:ethyl acetate 9:1). ***threo*-4e** oil; IR (neat) $\nu_{max}$ : 2956, 2927, 2869, 1708, 1491, 1452, 1377, 1115 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.70 (d, *J* = 6.2 Hz, 3H), 0.81 (t, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 6.2 Hz, 3H), 1.15-1.35 (m, 4H), 1.46-1.52 (m, 4H), 2.34-2.50 (m, 2H), 2.51-2.60 (m, 2H), 3.22 (sept, *J* = 6.2 Hz, 1H), 4.03 (d , *J* = 8.6 Hz, 1H), 4.44 (d , *J* = 8.6 Hz, 1H), 7.30 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.77 (q), 13.87 (q), 21.93 (t), 22.06 (t), 22.21 (q), 22.33 (q), 25.15 (t), 25.54 (t), 39.52 (t), 41.84 (t), 60.57 (d), 73.76 (d), 83.20 (d), 127.64 (d), 128.54 (d), 129.68 (d), 135.13 (s), 209.50 (s), 210.63 (s). HRMS (FAB) Calcd for $C_{21}H_{33}O_3$: 333.2429 Found: 333.2428. ***erythro*-4e** oil; IR (neat) $\nu_{max}$ : 2956, 2929, 2869, 1713, 1492, 1453, 1378, 1121, 1065 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.82 (m,6H), 1.09 (d, *J* = 6.1 Hz, 6H), 1.15-1.30 (m, 6H), 1.45-1.57 (m, 2H), 2.22 (m, 2H), 2.44 (m, 2H), 3.52 (sept, *J* = 6.1 Hz, 1H), 4.01 (d , *J* = 9.8 Hz, 1H), 4.49 (d , *J* = 9.8 Hz, 1H), 7.27 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.72 (q), 13.76 (q), 21.55 (q), 22.01 (t), 22.08 (t), 22.86

(q), 24.79 (t), 25.46 (t), 39.34 (t), 43.00 (t), 61.03 (d), 72.84 (d), 83.87 (d), 128.11 (d), 128.91 (d), 129.12 (d), 133.04 (s), 207.50 (s), 211.68 (s). HRMS (FAB) Calcd for $C_{21}H_{33}O_3$: 333.2429 Found: 333.2437.

*3,4-Dibutoxy-2,5-nonanedione* (**4f**). Methyllithium (2.0 mmol) was added at -78 °C to a stirred solution of **1a** (2.0 mmol) in ether (15 mL) and the mixture stirred at this temperature for 20 min. After reaching room temperature an excess of butyllithium (4.0 mmol) was added and the reaction mixture was treated by the usual work-up procedure. Column chromatographic purification of the oily residue with 99:1 hexane:ethyl acetate as eluent gave 372 mg of a *ca.* 1:1 mixture of *erythro*-**4f** and *threo*-**4f** (62% yield). Separation of the diastereomers was performed by HPLC with a reverse-phase column μBondapak and water:methanol (3:7) as eluent. The first compound eluted was ***erythro*-4f**: IR (neat) $\nu_{max}$ : 2955, 2929, 2869, 1715, 1463, 1350, 1096 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.89 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 1.27-1.41 (m, 6H), 1.45-1.62 (m, 6H), 2.27 (s, 3H), 2.51 (dt, *J* = 18.4, 7.4 Hz, 1H), 2.73 (dt, *J* = 18.4, 7.4 Hz, 1H), 3.27 (m, 2H), 3.54 (m, 2H), 4.00 (s, 2H); $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.77 (q x 2), 13.91 (q), 19.14 (t x 2), 22.30 (t), 24.85 (t), 27.50 (q), 31.61 (t x 2), 39.35 (t), 72.38 (t), 72.57 (t), 86.50 (d), 86.56 (d), 210.53 (s), 211.72 (s); HRMS (EI) Calcd for $C_{17}H_{32}O_4$: 300.2300. Found: 300.2310. ***threo*-4f**: IR (neat) $\nu_{max}$ 2956, 2928, 2869, 1717, 1463, 1350, 1109 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.94 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H), 1.27-1.47 (m, 6H), 1.50-1.68 (m, 6H), 2.23 (s, 3H), 2.57 (m, 2H), 3.54 (m, 4H), 3.98 (d, *J* = 3.6 Hz, 1H), 4.02 (d, *J* = 3.6 Hz, 1H), $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.82 (q x 2), 13.91 (q), 19.25 (t x 2), 22.29 (t), 24.93 (t), 27.38 (q), 31.84 (t x 2), 39.27 (t), 71.43 (t), 71.45 (t), 86.39 (d), 86.50 (d), 209.49 (s), 210.93 (s); HRMS (EI) Calcd for $C_{17}H_{32}O_4$: 300.2300. Found: 300.2310.

*3,4-Dibutoxy-1,2,5-triphenylpyrrole* (**6c**) To a stirred solution of **4c** (0.2 mmol) in 30 mL of $CHCl_3$, 0.1 mL of AcOH and 0.1 mL of aniline were added. The mixture was refluxed for 10 hours and, after reaching room temperature, the volatile solvents eliminated by distillation in vacuum. Purification of the crude mixture by preparative TLC (silicagel, hexane:ethyl acetate 9:1) gave 45 mg of **6c** (52% yield). Mp: 143°C (EtOH), IR (neat) $\nu_{max}$ : 3047, 2954, 2926, 2866, 1596, 1527, 1491, 1130, 1071, 1020 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) δ 0.79 (t, *J* = 7.2 Hz, 6H), 1.30 (sext, *J* = 7.2 Hz, 4H), 1.54 (m, 4H), 3.89 (t, *J* = 6.3 Hz, 4H), 6.85 (m, 2H), 7.05 (m, 13H); $^{13}C$ NMR ($CDCl_3$, 62.9 MHz) δ 13.79 (q), 19.12 (t), 32.09 (t), 73.70 (t), 121.1 (s), 125.80 (d), 126.44 (d), 127.46 (d), 128.42 (d), 128.93 (d), 129.72 (d), 130.93 (s), 137.00 (s), 138.49 (s); HRMS (EI) Calcd for $C_{30}H_{33}NO_2$: 439.2511 Found: 439.2515.

*(d,l-E)-2-Thienyl-2,3-di-n-butoxy-4-trimethylsilyloxy-4-(2-thienyl)-but-3-enylketone* (**7d**). To a solution of *E*-**5d** (0.1 mmol) in 6 mL of dry ether, 0.11 mmol of $^{t}$BuLi (1.7M in hexane) in 4 mL of ether were added at -78°C. The cooling bath was removed and after 10 min, chlorotrimethylsilane (0.3 mmol) in 5 mL of ether was added. The reaction mixture was stirred at room temperature for one hour and then hydrolyzed with 2 mL of a 10% aqueous $NaHCO_3$ solution. The organic layer was dried ($Na_2SO_4$) and the solvents removed in vacuum to afford 45 mg of an oily residue which was purified by TLC (silicagel, hexane:ethyl acetate 9:1) to give 38 mg (83% yield) of pure **7d**: oil; IR (neat) $\nu_{max}$ : 3090, 2955, 2930, 2870, 1678, 1510, 1458, 1410, 1249, 1095 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 0.20 (s, 9H), 0.84 (t, $J$ = 7.3 Hz, 3H), 0.94 (t, $J$ = 7.3 Hz, 3H), 1.29 (sext, $J$ = 7.3 Hz, 2H), 1.46 (sext, $J$ = 7.3 Hz, 2H), 1.55-1.77 (m, 4H), 3.75-4.00 (m, 4H), 5.84 (s, 1H), 6.99 (dd, $J$ = 4.9, 3.9 Hz, 1H), 7.07 (dd, $J$ = 4.9, 3.9 Hz, 1H), 7.25 (m, 2H); 7.59 (dd, $J$ = 4.9 , 1.1 Hz, 1H); 7.99 (dd, $J$ = 3.9, 1.1 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 0.17 (q), 13.83 (q), 14.01 (q), 18.99 (t), 19.29 (t), 31.87 (t), 32.17 (t), 71.78 (t), 73.84 (t), 74.34 (d), 125.49 (d), 126.22 (d), 126.25 (d), 127.67 (d), 133.46 (d), 134.05 (d), 135.96 (s), 140.50 (s), 141.23 (s), 143.83 (s) 191.26 (s). HRMS (EI) Calcd for $C_{23}H_{34}SiO_4S_2$: 466.1667 Found: 466.1668.

*Reaction of* **1a** *with MeLi at -78°C*. To a stirred solution of **1a** (2 mmol) in 15 mL of ether at -78°C , a solution of MeLi (6 mmol) in 10 mL of ether was dropwise added. The mixture was stirred at this temperature for 2 hours and then hydrolyzed with 2mL of a saturated solution of aqueous $NH_4Cl$. The cooling bath was removed and after reaching room temperature the layers were separated. The aqueous layer was extracted with ethyl acetate, the combined organic layers dried with $Na_2SO_4$ and the solvents removed in vacuum to give (based on NMR) a 2:1 mixture of cyclobutenediol **8a** and the diketones **4a**. Separation by column chromatography on silica gel and hexane:ethyl acetate as eluent (95:5 for elution of the less polar compounds and then 90:10) gave **4a** as a mixture of diastereomers (155 mg, 30%) and the hydroxycyclobutenone **9a** (202 mg, 55%). **8a**: $^1$H NMR: ($CDCl_3$, 250MHz) δ 0.85 (t, 6H), 1.3 (s, 6H), 1.2-1.4 (m, 4H), 1.4-1.6 (m, 4H), 3.9 (t, 4H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 13.60 (q), 18.74 (t), 18.98 (q), 31.56 (t), 69.86 (t), 77.38 (s), 132.33 (s). **9a**: oil, IR (neat) $\nu_{max}$ : 3529, 2957, 2928, 2871, 1763, 1604, 1381, 1306, 1179, 1069 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 250 MHz) δ 0.91 (t, $J$ = 7.3 Hz, 3H), 1.37 (sext, $J$ = 7.3 Hz, 2H), 1.42 (s, 3H) 1.61 (m, 2H), 2.03 (s, 3H), 4.21 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 62.9 MHz) δ 8.73 (q), 13.64 (q), 18.64 (t), 19.02 (q), 31.71 (t), 70.21 (t), 85.29 (s), 152.33 (s), 156.01 (s), 191.74 (s); HRMS (CI) Calcd for $C_{10}H_{17}O_3$: 185.1177. Found: 185.1180.

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