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Short Report

Short Synthesis of a New Cyclopentene-1,3-dione Derivative Isolated from *Piper carniconnectivum*

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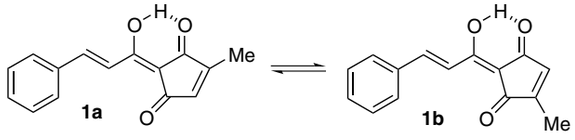
A síntese total da ciclopentenodiona (**1**), isolada das raízes de *Piper carniconnectivum*, é descrita em 8 etapas e 11% de rendimento global a partir do 2-acetilfurano, fornecendo uma mistura 57:43 dos dois possíveis isômeros geométricos **1a** e **1b**.

The total synthesis of cyclopentene-1,3-dione (**1**), a new natural cyclopentenedione derivative isolated from the roots of *Piper carniconnectivum*, is described in 8 steps and 11% overall yield from 2-acetylfuran, giving a 57:43 mixture of the two possible geometric isomers **1a** and**1b**.

Keywords: aldol reaction, allylic alcohol oxidation, cyclopentenedione derivative, *Piper carniconnectivum*

Introduction

The cyclopentenedione (**1a/1b**) (Figure 1) is a new natural cyclopentenedione derivative that was isolated recently by Braz-Filho and coworkers[1] from the roots of a specimen of *Piper carniconnectivum*, collected in Porto Velho, Rondônia, in the northern part of Brazil. This specimen belongs to the tropical *Piperaceae* family, that comprises many important plants, very useful in folk medicine as bioproducers of essential oils.[2,3] The structure of cyclopentenedione derivative (**1**) was established by spectroscopic data, mainly 1D and 2D NMR as well as by Electron Impact Mass Spectrometry (EIMS).[1] According to the authors,[1] the isolated cyclopentenedione derivative may have structure **1a** or **1b** or even exist as an equilibrium mixture between these two enol forms showing average ^{1}H and ^{13}C NMR spectra due to a proposed rapid interconversion between **1a** and **1b**.



cyclopentenedione (**1**)

Figure 1. Enol forms of cyclopentenedione derivative (**1**).

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Dedicated to Prof. Raimundo Braz-Filho for his outstanding contributions to the field of Organic Chemistry in Brazil.

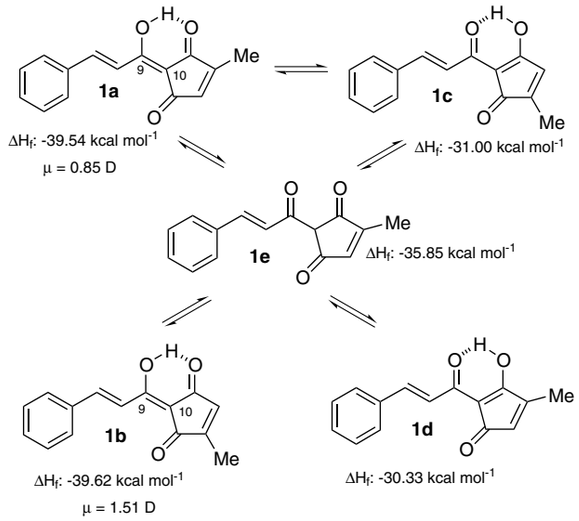
In connection with our interest in the total synthesis of natural products isolated from Brazilian sources, we became interested in the synthesis of the cyclopentenedione derivative (**1**). An efficient and flexible synthesis of this very interesting natural product is important to provide further material for biological studies, along with access to novel analogues, as well as to prove the assignment given by Braz-Filho and coworkers.[1] The approach described here to the cyclopentenedione derivative (**1**) might give access to additional derivatives with potential relevance to biological studies.

Results and Discussion

Theoretical calculations

At the beginning, we were intrigued by the proposed equilibrium between enol forms **1a** and **1b**, and by the fact that this rapid equilibrium would lead to average ^{1}H and ^{13}C NMR spectra. At first we decided to evaluate the thermodynamic stability of enol forms **1a-d** when compared to triketone **1e** (Scheme 1). The heat of formation (ΔH_f) obtained by AM1 semiempirical calculations (using PC Spartan Plus) of compound **1e** was compared with those of possible enols **1a-d** and is outlined in Scheme 1.

The calculated heats of formation confirmed that the enol forms **1a** and **1b**, and not the enol forms **1c** and **1d**, were the thermodynamically favorable structures. We believe that the antiaromatic electronic structure of the

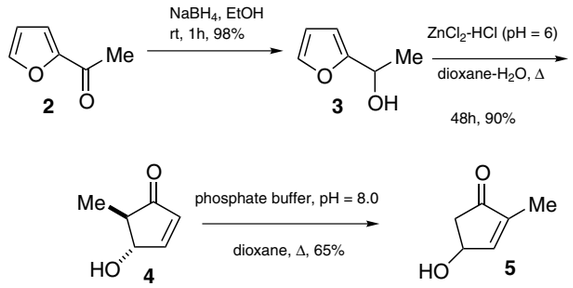


Scheme 1.

cycles in enol forms **1c** and **1d** explains the absence of these tautomers in solution, as proposed by Braz-Filho and coworkers.[1] The difference in the heats of formation for enol forms **1a** and **1b** is very small. We first suspected of structure **1a** as being the natural product in view of the larger calculated dipole moment for **1b** (1.51 D) in comparison with that of **1a** (0.85 D). It is also interesting to observe that the most stable enol forms **1a** (C9-C10, *Z*) and **1b** (C9-C10, *E*) are more stable than triketone **1e** by 3.69 and 3.77 kcal mol^{-1}, respectively.[4] We believe that these differences are too large to allow a rapid interconversion between enol forms **1a** (*Z* isomer) and **1b** (*E* isomer) at room temperature. Based on these results we believed that the geometric C9-C10 isomers **1a** and **1b** should not be present in a rapid equilibrium, the ^{1}H and ^{13}C NMR spectra should not be an average of these two forms, and that Braz-Filho and coworkers had isolated one of the two isomeric compounds, **1a** or **1b**.

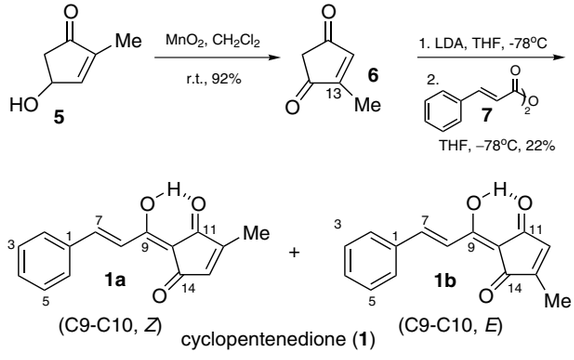
Synthetic results

Our approach to cyclopentenedione derivative (**1**) started with the preparation of furylmethylcarbinol (**3**) by the reduction of commercially available 2-acetylfuran (**2**) with $NaBH_4$ (Scheme 2).[5] Compound **3** was isolated in 98% yield and transformed into 4-hydroxy-5-methyl-cyclopenten-2-one (**4**) in 90% yield after treatment with $ZnCl_2$-HCl (pH 6.0) under reflux in dioxane-H_2O for 48 h.[6] Upon treatment of 4-hydroxy-5-methylcyclopenten-2-one (**4**) with phosphate buffer (pH 8.0) in refluxing dioxane for 24 h, 4-hydroxy-2-methylcyclopenten-2-one (**5**) was obtained in 65% yield.[7] By using this strategy we were able to prepare up to gram quantities of hydroxyketone **5**.



Scheme 2.

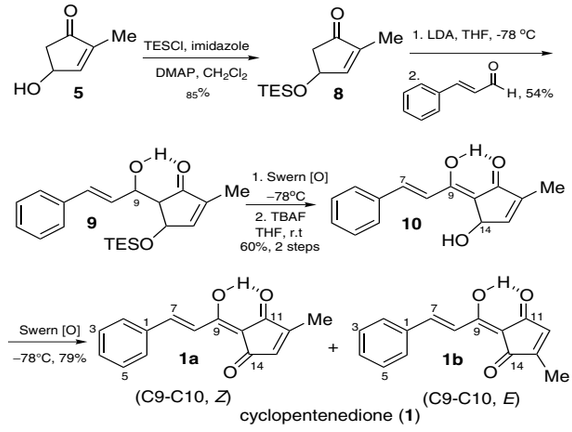
Diketone **6** was obtained in almost quantitative yield by the smooth oxidation of hydroxyketone **5** with MnO_2 (Scheme 3).[8,9] At this point, all that remained was to carry out the necessary acylation coupling. It was with some gratification that we observed that the reaction between lithium enolate of diketone **6** and cinnamic anhydride **7** gave a 57:43 mixture of cyclopentenediones **1a/1b** in 22% yield, after purification by flash column chromatography, together with starting material and by-products arising from O-acylation (Scheme 3).



Scheme 3.

In order to try to improve the yields for formation of **1a/1b**, we tested a new synthetic route (Scheme 4). Protection of the OH-functionality in **5** with TESCl and imidazole at room temperature gave ketone **8** in 85% yield. Treatment of **8** with LDA in THF at –78 °C, followed by slow addition of cinnamaldehyde, gave aldol adduct **9** as a mixture of diastereoisomers. Oxidation of the OH-function at C9 in allylic alcohol **9** under standard Swern[11] conditions followed by removal of the TES protecting group with TBAF in THF led to diol **10** in 60% overall yield. The last step involved treatment of diol **10** under standard Swern oxidation conditions, to give a 59:41 mixture of **1a/1b** in 79% yield.[11]

The spectroscopic and physical data [^{1}H and ^{13}C NMR, IR, MP (Table 1)] for the major component of the 59:41



Scheme 4.

mixture present in the synthetic material were identical in all respects with the published data for natural cyclopentenedione derivative. In the synthetic material, we were able to observe additional new signals corresponding to the possible geometric isomer.[1]

In fact, both isomers, **1a** (C9-C10, *E*) and **1b** (C9-C10, *Z*) revealed very similar ^{1}H and ^{13}C NMR spectra. This result is in agreement with the small difference in the heats of formation for enol forms **1a** and **1b**.

We observed two doublets for the CH_3 groups at C12, at 2.12 and 2.11 ppm, respectively, both with coupling constants equal to 1.6 Hz (Figure 2). The doublet in 2.12 corresponds to the methyl group found in the natural product, as described by Braz-Filho and coworkers.[1]

Other noteworthy observations from this spectrum are two quartets at 6.70 and 6.61 ppm, with coupling constants equal to 1.6 Hz (Figure 3). The quartet at 6.70 ppm corresponds to the quartet found in the natural product.

We were also able to observe two different broad signals at 12.11 and 11.99 ppm, corresponding to the hydrogens

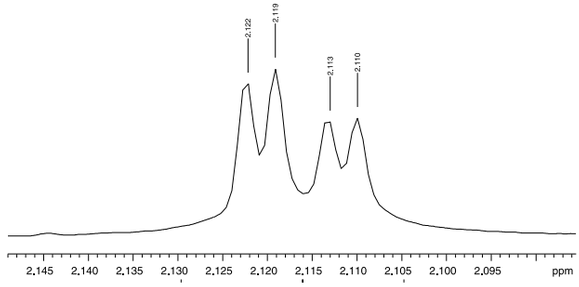


Figure 2. Expansion of the methyl resonances (δ 2.11 and 2.12) for synthetic **1a/1b**.

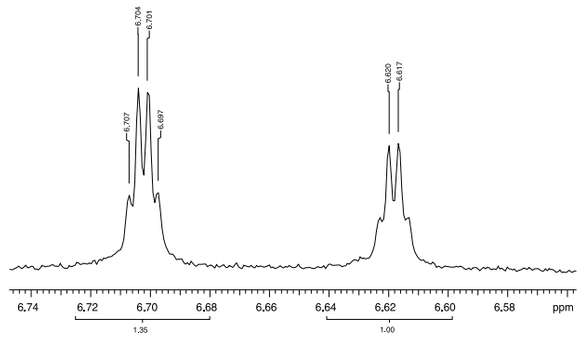


Figure 3. Expansion of the vinylic resonances (δ 6.70 and 6.61) for synthetic **1a/1b**.

Table 1. Comparison of ^{1}H and ^{13}C NMR data ($CDCl_3$) for synthetic and authentic cyclopentenedione **1a/1b**[1]

Position	^{1}H δ (ppm),mult. J [Hz] Synthetic cyclopentenedione derivative 500 MHz	^{1}H δ (ppm),mult. J [Hz] Authentic cyclopentenedione derivative[1] 500 MHz	^{13}C, δ (ppm) Synthetic cyclopentenedione derivative 125 MHz	^{13}C, δ (ppm) Authentic cyclopentenedione derivative[1] 125 MHz
1	—	—	134.8	135.2
2	7.67-7.65, m	7.67-7.65, m	129.0	129.5
3	7.44-7.42, m	7.44-7.42	128.7	129.4
4	7.44-7.42, m	7.44-7.42	130.7	131.1
5	7.44-7.42, m	7.44-7.42	128.7	129.4
6	7.67-7.65, m	7.67-7.65, m	129.0	129.5
7	7.80* and 7.79, d, 16.2	7.79, d, 16.0	143.3 and 143.2*	143.5
8	7.73 and 7.72*, d, 16.2	7.75, d, 16.0	117.6 and 117.5*	117.9
9	—	—	168.0 and 167.7*	168.1
10	—	—	103.3 and 103.1*	103.5
11	—	—	201.3 and 200.7*	201.1
12	—	—	158.1 and 154.1*	158.5
13	6.70 and 6.61*, q, 1.5	6.70, q, 1.60	140.7* and 137.0	137.4
14	—	—	192.3 and 191.8*	192.6
15	2.12 and 2.11*, d, 1.5	2.12, d, 1.60	11.4 and 10.6*	11.8
OH	12.11 and 11.99*, m	12.11, br s	—	—

* A signal marked with (*) corresponds to the minor isomer.

bonded to the OH in enol forms **1a** and **1b** (Figure 4). These new signals at 2.11, 6.61 and 112.99 ppm are strong evidence in favor of the presence of the other geometric isomer. The chemical shift for the signals at 11.99 and 12.11 ppm do not change with dilution or with temperature.

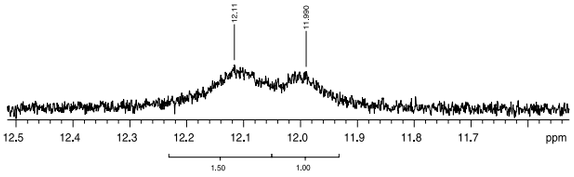


Figure 4. Expansion of the OH resonance (δ 11.99 and 12.11) for synthetic **1a/1b**.

Looking carefully at the ^{1}H NMR spectra of compound **1a/1b**, kindly sent by Braz-Filho and coworkers, we were able to confirm that exactly the same signals at 2.11 and 6.61 ppm, as very small peaks, are present in the original spectra of the natural product (Figures 5 and 6). This lead to the conclusion that the natural product was isolated as a >95:5 mixture of the two isomers.

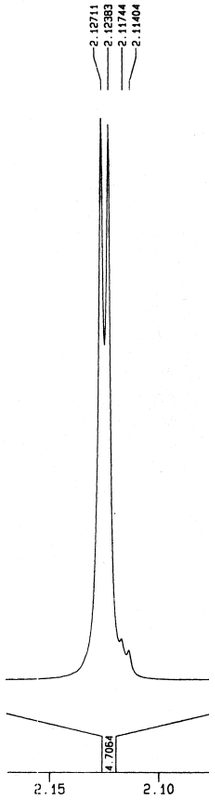


Figure 5. Expansion of the methyl resonance (δ 2.11 and 2.12) for natural **1a/1b**.

We have acquired ^{1}H and ^{13}C NMR spectra of a $CDCl_3$ solution of a 57:43 mixture of **1a/1b** at 25 °C as well as at

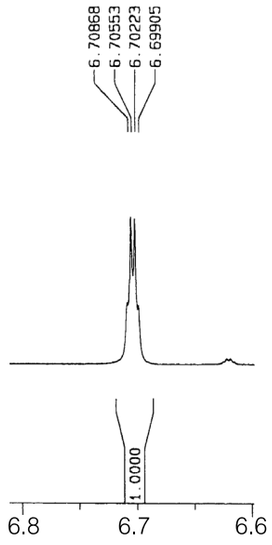


Figure 6. Expansion of the vinylic resonance (δ 6.70 and 6.61) for natural **1a/1b**.

60 °C and observed that these spectra did not change with time, with the NMR being identical even after 30 days in the NMR tube. Acquisition of the ^{1}H NMR spectra in DMF-d6 at room temperature and at 140 °C proved to be very interesting. At 25 °C, we have observed two signals related to the vinylic hydrogens of both isomers at 6.9 and 7.2 ppm. At 140 °C, these signals coalesce to a single broad signal at 7.0 ppm, showing that only at high temperature we can observe an average NMR spectrum.

On the other hand, we have tried to separate the two isomers in order to get a crystal of one of them to carry out an X-ray crystallographic analysis but, unfortunately, that was not possible, since they are not separable by flash column chromatography. However, we were able to isolate a fraction enriched with one isomer in a 34:66 ratio. This is shown in Figures 7-9 with expansions taken from a sample of this mixture.

We have acquired the ^{1}H NMR of this sample again after two days and have observed that this changed to the same 57:33 ratios observed before (Figures 2 to 4). In acidic $CDCl_3$, an equilibrium exists between these enol forms and this equilibrium favors the natural product. Based on these results, we strong believe that Braz-Filho and coworkers isolated one isomer, and that the minor signals in their NMR spectra correspond to the unnatural isomer, and that the NMR in acidic $CDCl_3$ shows the other isomer being formed in small amounts. We believe that even in the case of the natural product a long exposition in the NMR tube with $CDCl_3$ as solvent would lead to the same 57:33 equilibrium ratio.

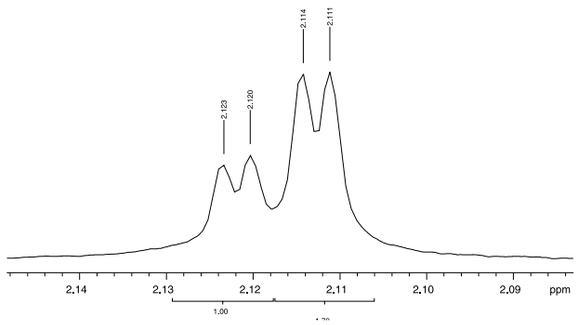


Figure 7. Expansion of the methyl resonances (δ 2.12 and 2.11) for synthetic **1a/1b** after SiO_2 column chromatography.

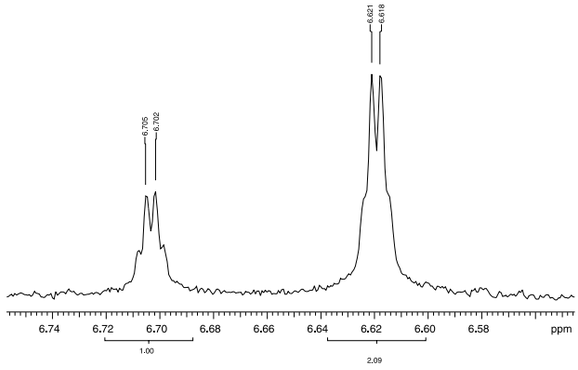


Figure 8. Expansion of the vinylic hydrogen resonance (δ 6.70 and 6.61) for synthetic **1a/1b** after SiO_2 column chromatography.

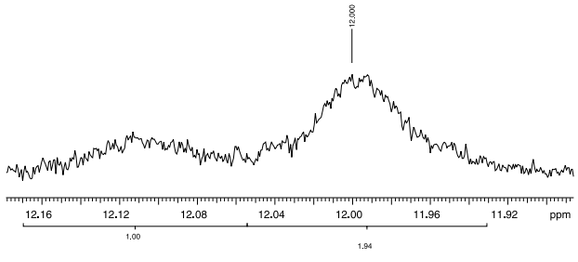
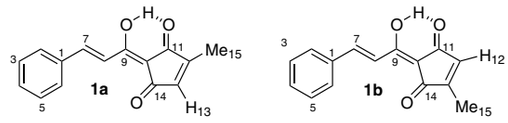


Figure 9. Expansion of the OH resonance (δ 12.1 and 12.0) for synthetic **1a/1b** after SiO_2 column chromatography.

The correct structure for the natural product was confirmed as being **1a** by the heteronuclear long-range coupling ($^nJ_{CH}$; n = 2,3,4) obtained by HMBC experiments in $CDCl_3$ as solvent. Heteronuclear long-range coupling of C11 (δ_C 201.3) with H13 (δ_H 6.70, $^3J_{CH}$) and H15 (δ_H 2.12, $^3J_{CH}$), as well as between C14 (δ_C 191.8) with H13 (δ_H 6.70, $^2J_{CH}$) and H15 (δ_H 2.12, $^4J_{CH}$) for **1a**, together with the long-range coupling of C11 (δ_C 200.7) with H12 (δ_H 6.61, $^2J_{CH}$) and H15 (δ_H 2.11, $^4J_{CH}$), as well as between C14 (δ_C 192.3) with H12 (δ_H 6.61, $^3J_{CH}$) and H15 (δ_H 2.11 ppm, $^3J_{CH}$) for **1b**, unambiguously established the correct structure as being **1a** (Figure 10).



1a, C11 (δC 201.3) with H13 (δ_H 6.70, $^3J_{CH}$) and H15 (δ_H 2.12, $^3J_{CH}$)
1a, C14 (δC 191.8) with H13 (δ_H 6.70, $^2J_{CH}$) and H15 (δ_H 2.12, $^4J_{CH}$)

1b, C11 (δC 200.7) with H12 (δ_H 6.61, $^2J_{CH}$) and H15 (δ_H 2.11, $^4J_{CH}$)
1b, C14 (δC 192.3) with H12 (δ_H 6.61, $^3J_{CH}$) and H15 (δ_H 2.11, $^3J_{CH}$)

Figure 10. Heteronuclear 2D shift-correlated obtained by ^1H-^{13}C-COSY-^nJCH (n = 2,3,4 HMBC) experiments in $CDCl_3$ as solvent.

Conclusions

Our approach required 8 steps from commercially available 2-acetylfuran and produced the desired product in 11% overall yield. The results of extensive application of 2D NMR spectral techniques were used to determine the correct structure for the natural product as being **1a**. This synthesis confirms the assignment of Braz-Filho and coworkers[1] and, as a result, the route to cyclopentenedione derivative (**1**) presented here is, in principle, readily applicable for the preparation of additional analogs with potential relevance to biological sudies.[12] Studies are underway in order to further improve the synthesis of cyclopentenedione (**1**) and the results will be described in due course.

Experimetal

All reactions were carried out under an atmosphere of argon or nitrogen in flame-dried glassware with magnetic stirring. Dichloromethane was distilled from CaH_2. THF, diethyl ether and toluene were distilled from sodium/benzophenone ketyl. Cynnamaldehyde was distilled immediately prior to use. ^{i}PrOH was distilled from $Mg(^iPrO)_2$. TLC plates were obtained of silica gel 60 and GF (5-4 μm thickness) and visualization was accomplished with either a UV lamp or I_2 staining. Chromatography on silica-gel (Aldrich, 230-400 mesh) was performed using a forced-flow of the indicated solvent system (flash chromatography). Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain or phosphomolybdic acid followed by heating or I_2 staining. ^{1}H NMR spectra were recorded on either a Varian Gemini 300 (300 MHz) or a Varian Inova 500 (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 ppm) unless otherwise indicated. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, st = sextet, ap t = apparent triplet, m = multiplet, b = broad, br s = broad singlet, br d = broad

doublet, dd = doublet of doublets, coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on either a Varian Gemini 300 (75 MHz) or Bruker AC 300/P (75 MHz) spectrometers and are recorded in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm or C_6D_6 at 128 ppm) unless otherwise indicated. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on GC/MS HP-5988-A.

*2-Furylmethylcarbinol (**3**)*

Procedure 1. Furan (2.7 mL, 37 mmol) was measured into a dry round-bottom flask equipped with a magnetic stirrer and containing freshly distilled ether (20 mL) under argon atmosphere. The flask was cooled to –25 °C, and *n*-BuLi in hexanes (7.9 mL, 2.3 mol L^{-1}, 18 mmol) was added dropwise from a syringe. The flask was allowed to warm to 0 °C, the cold bath was removed, and the reaction mixture was stirred 4 h at room temperature. The reaction mixture was cooled back to –25 °C, and acetaldehyde (4 mL, 73 mmol) was added dropwise *via* syringe. After being allowed to warm to room temperature over a period of 3 h, the reaction mixture was neutralized with cold saturated NH_4Cl solution (5 mL). The organic layer was separated, and aqueous layer was extracted with ether (2 x 5 mL). The combined organic phase was dried ($MgSO_4$) and passed through a silica gel plug to remove polar impurities, after which TLC analysis showed the presence of a single component. The solution was concentrated and dried *in vacuo* to give 1.7 g (84%) of 2-furylmethylcarbinol (**3**) as an orange liquid (used without further purification).

Procedure 2. To a solution of 2-acetyl furan (**2**) (1.0 g, 9.09 mmol) in ethanol (20 mL), at 0 °C, was slowly added $NaBH_4$ (0.19 g, 5.0 mmol). The reaction mixture was let to stir at room temperature for 2 h and the solvent was removed under reduced pressure. After filtration in a plug of silica, 2-furylmethylcarbinol (**3**) (1.036 g, 98%) was isolated as an orange liquid (used without further purification). R_f 0.25 (20% EtOAc/hexanes); IR (film) ν_{max}/cm^{-1}: 3352, 2982, 1721, 1625, 1506, 1451, 1372, 1231; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* 1.8, 0.7 Hz, 1H), 6.33 (dd, *J* 3.3, 1.8 Hz, 1H), 6.23 (d, *J* 3.3 Hz 1H), 4.89 (q, *J* 6.6 Hz, 1H), 2.12 (br s, 1H), 1.55 (d, *J* 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 141.8, 110.8, 105.1, 63.1, 21.2.

*4-Hydroxy-2-methyl cyclopenten-2-one (**5**)*

To a solution of (2-furyl)-methylcarbinol (**3**) (1.0 g, 8.9 mmol) in 1,4-dioxane (54 mL) was added a solution of $ZnCl_2$ (4.47 g, 32.9 mmol) in H_2O (36 mL), and pH was then adjusted to 5.0 with 0.1 mol L^{-1} HCl. The mixture was refluxed for 24 h. After cooling to ambient temperature, the solvent was evaporated under reduced pressure and the aqueous phase was extracted with EtOAc (3 x 40 mL). The combined extracts were washed with sat. $NaHCO_3$ and sat. NaCl solutions and finally dried with $MgSO_4$. Evaporation of the solvent gave crude 4-hydroxy-5-methylcyclopentenone (**4**) (90%, red oil); R_f 0.26 (25% EtOAc/hexane). Crude 4-hydroxy-5-methylcyclopentenone (**4**) was dissolved in 1,4-dioxane (60 mL) and a phosphate buffer solution (pH 7.9, 60 mL) was added. The mixture was refluxed for 24 h and more phosphate buffer solution (pH 7.9, 40 mL) was added. The solution was refluxed for an additional 24 h and after cooling to rt the solvent was removed under reduced pressure. The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (60 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the resulting oil was chromatographer on silica gel (EtOAc/hexane, 2:1) to give 4-hydroxy-2-methylcyclopentenone (**5**) (0.65 g, 65%, yellow oil). R_f 0.22 (50% EtOAc/hexane); IR (film) ν_{max}/cm^{-1}: 3400, 1710, 1640; ^1H-NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 1H), 4.94 (m, 1H), 2.80 (dd, *J* 18.7, 6.0 Hz, 1H), 2.31 (br s, 1H), 2.30 (dd, *J* 18.7, 1.8 Hz, 1H), 1.80 (t, *J* 1.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 206.3, 156.6, 143.5, 68.4, 44.5, 10.0.

*4-Methyl-4-cyclopentene-1, 3-dione (**6**)*

To a solution of 4-hydroxy-2-methylcyclopentenone (**5**) (0.5 g, 4.45 mmol) in CH_2Cl_2 (20 mL) was added MnO_2 (7.75 g, 89 mmol) at room temperature. The resulting mixture was stirred at room temperature for 1 h, passed through a celite plug and concentrated. Purification by silica gel column chromatography (10% EtOAc in hexane) gave 4.5 g (92%) of cyclopentenedione (**6**) as a yellow solid. R_f 0.36 (40% EtOAc/hexane); IR (film) ν_{max}/cm^{-1}: 3430, 3081, 2927, 1703, 1684, 1380, 1251; ^1H-NMR (300 MHz, $CDCl_3$) δ 7.01 (q, *J* 1.4 Hz, 1H), 2.90 (s, 2H), 2.12 (d, *J* 1.4 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 201.0, 199.2, 162.3, 146.0, 41.7, 11.3.

*2-Methyl-4-(triethylsilyloxy)cyclopent-2-enone (**8**)*

To a stirred solution of hydroxy ketone **5** (0.127 g, 1.0 mmol) in CH_2Cl_2 (4 mL) at –5 °C was added imidazole (0.086 g, 1.31 mmol), triethylsilylchloride (0.166 g, 1.1 mmol) and catalytic amounts of *N,N*-dimethylaminopyridine and stirring was continued for 1 h. The reaction mixture was partitioned between EtOAc (5 mL) and H_2O (5 mL) then the organic layer was washed with

brine, dried over anhydrous $MgSO_4$, filtered and evaporated. Purification of the crude product on silica gel with 5% EtOAc:hexanes as eluant gave the silyl ether **8** (0.192 g, 85%) as a colorless oil. R_f 0.32 (5% EtOAc/hexane); IR (film) ν_{max}/cm^{-1}: 3478, 3414, 2961, 2917, 2873, 1723, 1646, 1461, 1413; ^{1}H NMR (300 MHz, C_6D_6) δ 6.63 (m, 1H), 4.36 (m, 1H), 2.46 (dd, *J* 17.9, 5.9, Hz, 1H), 2.21 (dd, *J* 17.9, 2.2 Hz, 1H), 1.64 (t, *J* 1.5 Hz, 3H), 0.98 (t, *J* 8.0 Hz, 9H), 0.54 (q, *J* 8.0 Hz, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 204.2, 156.4, 128.0, 69.0, 45.4, 7.2, 5.3, 0.3.

*2-[1-Hydroxy-3phenyl-(Z,2E)-2-propenylidene]-4-methyl-4-cyclopentene-1,3-dione (**1**)*

*From diketone (**6**).* A solution of diisopropylamine (0.31 mL, 2.2 mmol) in 4 mL of THF was cooled under argon in an ice bath, and *n*-butyl lithium 2.56 mol L^{-1} (0.86 mL, 2.2 mmol) in hexane was added. The resulting solution was stirred at 0 °C for 15 min, cooled to –78 °C, and a solution of ketone **6** (0.22 g, 2.0 mmol) in 1 mL of THF was added dropwise. After 45 minutes at –78 °C, a solution of cinnamic anhydride (**7**) (0.441 g, 3.0 mmol) in 2 mL of THF was added dropwise. The resulting mixture was stirred at –78 °C for 45 min, poured into aqueous NH_4Cl, and extracted with ether (2 x 10 mL). The combined organic extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a yellow solid which was purified by silica gel column chromatography (10% EtOAc in hexane) to provide 0.106 g (0.44 mmol, 22%) of the cyclopentenedione derivative (**1**) as a yellow solid.

*From Ketone (**8**).* A solution of diisopropylamine (0.155 mL, 1.1 mmol) in 3 mL of THF was cooled under argon in an ice bath, and *n*-butyl lithium 2.56 mol L^{-1} (0.43 mL, 1.1 mmol) in hexane was added. The resulting solution was stirred at 0 °C for 15 min, cooled to –78 °C, and a solution of ketone **8** (0.226 g, 1.0 mmol) in 1 mL of THF was added dropwise. After 45 minutes at –78 °C, a solution of cinnamaldehyde (0.38 mL, 3.0 mmol) in 1 mL of THF was added dropwise. The resulting mixture was stirred at –78 °C for 45 min, poured into aqueous NH_4Cl, and extracted with ether (2 x 10 mL). The combined organic extracts were washed with 10 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a yellow oil which was purified by silica gel column chromatography (10% EtOAc in hexane) to provide 0.193 g (0.54 mmol, 54%) of the aldol adduct (**9**) as a yellow solid. To a solution of 0.12 mL (1.67 mmol) of DMSO in 4 mL of CH_2Cl_2 at –78 °C was added 0.11 mL (1.28 mmol) of oxalyl chloride (gas evolution). After 10 min, a solution of 0.193 g (0.54 mmol) of aldol adduct **9** in 2 mL of CH_2Cl_2 was added forming a cloudy white mixture. This was stirred for 15 min at –78 °C then 0.37 mL (2.66 mmol) of triethylamine was added. The reaction was stirred at –78 °C for 40 min then quenched by the addition of 5 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to ambient temperature then diluted with 10 mL of CH_2Cl_2. The layers were separated and the aqueous phase was extracted with two 10 mL portions of CH_2Cl_2. The combined organic extracts were washed with 10 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. ^{1}H NMR spectroscopy of the unpurified diketone was very clean. To a solution of the previously prepared diketone in 2 mL of THF, at ambient temperature was added 2.5 mL (2.5 mmol) of a 1.0 mol L^{-1} solution of TBAF in THF. The reaction mixture was stirred at ambient temperature for 16 h then concentrated *in vacuo*. The crude product was purified by flash chromatography (EtOAc:hexanes 25%) as eluant to give diketone **10** (0.078 g, 60% over two steps) as a yellow oil. To a solution of 0.07 mL (1.0 mmol) of DMSO in 3 mL of CH_2Cl_2 at –78 °C was added 0.07 mL (0.78 mmol) of oxalyl chloride (gas evolution). After 10 min, a solution of 0.078 g (0.324 mmol) of alcohol **10** in 2 mL of CH_2Cl_2 was added forming a cloudy white mixture. This was stirred for 15 min at –78 °C then 0.22 mL (1.62 mmol) of triethylamine was added. The reaction was stirred at –78 °C for 40 min then quenched by the addition of 5 mL of saturated aqueous NH_4Cl. The mixture was allowed to warm to ambient temperature then diluted with 5 mL of CH_2Cl_2. The layers were separated and the aqueous phase was extracted with two 5 mL portions of CH_2Cl_2. The combined organic extracts were washed with 5 mL of brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give 0.062 g (0.26 mmol, 79%) of the cyclopentenedione derivative (**1**) as a yellow solid. R*f* 0.37 (30% EtOAc/Hexane); IR (film) ν_{max}/cm^{-1}: 3428, 2965, 1632, 1589, 1266, 1103, 1023, 803, 742, 699; (HRMS) Exact mass calc. for $C_{15}H_{12}O_3$: 240.0786. Found: 240.0787.

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References

1. Facundo, V. A.; Sá , A. L.; Silva, S. A. F.; Morais, S. M.; Matos, C. R. R.; Braz-Filho, R.; *J. Braz. Chem. Soc.* **2004**, *15*, 140.
2. Ribeiro, J. E. L. da S.; Hopkins, M. J. G.; Vincentin, A.; Sothers, C. A.; Costa, M. A. da S.; de Brito, J. M.; de Souza, M. A. D.; Martins, L. H. P.; Lohmann, L. G.; Assunção, P. A. C. L.; Pereira, E. da C.; Mesquita, M. R.; Procópio, L. C.; *Flora da Reserva Ducke – Guia de Identificação das Plantas Vasculares de uma Floresta de Terra-Firme na Amazônia Central*, INPA-DFID: Manaus, Amazonas, Brasil, 1999. p. 181.
3. For other compounds isolated from the *Piper* genus, see: Parmar, V. S.; Jain, S. C.; Bisht, K. S.; Jain, R.; Taneja, P.; Jha, A.; Tyagi, O. D.; Prasad, A. K.; Wengel, J.; Olsen, C. E.; Boll, P. M.; *Phytochemistry* **1997**, *46*, 597.
4. The numbering of (**1**) as well as of each intermediate follows that suggested in reference 1.
5. West, F. G.; Gunawardena, G. U.; *J. Org. Chem.* **1993**, *58*, 2402. Furylcarbinol (**5**) could also be obtained by the reaction of 2-lithium furan with acetaldehyde in 84% yield.
6. Piancatelli, G.; Scettri, A.; David, G.; D'Auria, M.; *Tetrahedron* **1978**, *34,* 2775; West, F. G.; Gunawardena, G. U.; *J. Org. Chem.* **1993**, *58*, 5043; Piancatelli, G.; D'Auria, M.; D'Onofrio, F.; *Synthesis* **1994**, 867.
7. Scettri, A.; Piancatelli, G.; D'Auria, M.; David, G.; *Tetrahedron* **1979**, *35,* 135; Shono, T.; Hamaguchi, H.; Aoki, K.; *Chem. Lett.* **1977**, 1053; Csáky, A. G.; Mba, M.; Plumet, J.; *J. Org. Chem.* **2001**, *66*, 9026; Csáky, A. G.; Mba, M.; Plumet, J.; *Synlett* **2003**, 2092.
8. Corey, E. J.; Gilman, N. W.; Ganem, B. E.; *J. Am. Chem. Soc*. **1968**, 90, 5616.
9. For large scale preparations of cyclopentenedione **12**, the use of Jones oxidation conditions is recommended. See: Lola, D.; Belakovs, S.; Gavars, M.; Turovskis, I.; Kemme, A.; *Tetrahedron* **1998**, *54*, 1589.
10. Olivieri, A. C.; González-Sierra, M.; Rúveda, E.; A.; *J. Org. Chem.* **1986**, *51*, 2824.
11. Mancuso, A. J.; Swern, D.; *Synthesis* **1981**, 165.
12. New compounds and the additional isolated intermediates gave satisfactory ^{1}H and ^{13}C NMR, IR, HRMS and analytical data. Yields refer to chromatographically and spectroscopically homogeneous materials.

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