Convergent Approaches to Saudin Intermediates

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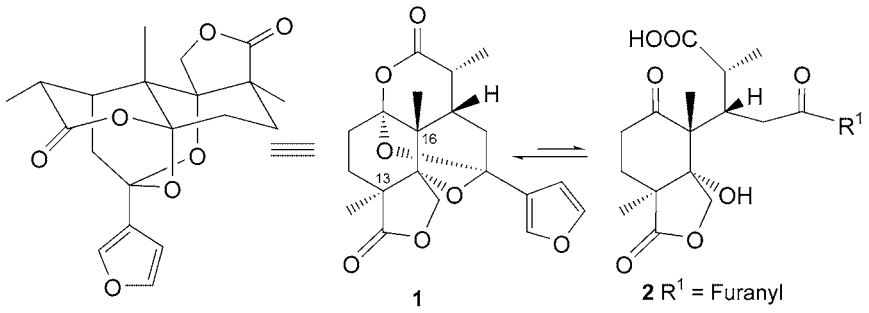
Different convergent approaches to the highly oxygenated sesquiterpene natural product saudin (**1**), has been investigated. Our strategy has included a *Michael* addition and aldol condensation reaction as key steps. During the synthetic development, we have found serious steric hindrance when an α-Me-substituted alkyl vinyl ketone was used. Such steric hindrance has been overcome by synthesizing the vinyl ketone **16** through an anionic fragmentation, which was carefully studied. Finally, the intermediate **18** has been synthesized in a one-pot reaction from the vinyl ketone **16** and has been cyclized to obtain the promising tricyclic intermediate **20**.

Introduction. – Saudin (**1**) is a natural product, which belongs to a group of terpenoids isolated from the leaves of the toxic plant *Cluytia richardiana* [1][2]. This compound shows a unique rearranged labdane skeleton, which contains seven stereogenic centers, six of which are consecutive. Saudin (**1**) shows potent hypoglycemic activity. The structural complexity of **1** has stimulated interest in its total synthesis [3–6]. Few years ago, *Winkler* and *Doherty* [7] carried out the first total synthesis of **1** in 15 steps, the key step being an intramolecular dioxenone photocycloaddition.



1 **2** R^1 = Furanyl

Recently, *Boeckman et al.* [8] have reported the first enantioselective total synthesis of (+)- and (−)-saudin and the corresponding absolute configurations. The core of their synthetic approach was the use of a *Lewis* acid mediated stereoselective *Claisen* rearrangement to introduce the correct configuration at the two quaternary C-atoms (C(13) and C(16)).

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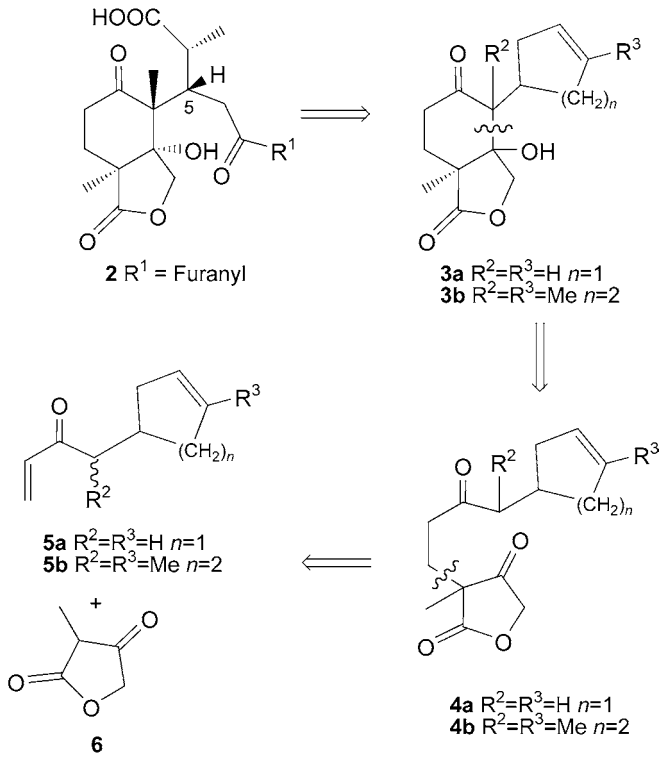
Following our efforts to develop strategies toward the synthesis of polyoxygenated natural products [9–12], we were interested in the synthesis of **1** due to its structural complexity and biological properties [13][14]. Here, we describe our efforts on the stereoselective synthesis of an advanced tricyclic key intermediate **3** that can lead to **1**.

The retrosynthetic analysis for our synthetic approach is shown in *Scheme 1*. This analysis was based upon the hypothesis proposed by *Mossa et al.* [1], where **1** is assumed to be in equilibrium with its open form. Therefore, we envisioned the synthesis of this natural product through the open form by a spontaneous or acid-catalyzed cyclization. The key intermediate **2** could be prepared by the oxidative cleavage of **3a** or **3b**. Compounds **3a** or **3b**, in turn, can be generated from **4a** or **4b**, respectively, by sequential *Michael* addition and aldol condensation. The compounds **4a** or **4b** can be derived by *Michael* addition of methyl vinyl ketones **5a** or **5b**, respectively, to 2,3,4,5-tetrahydro-3-methylfuran-2,4-dione (**6**), respectively (*Scheme 1*). The tricyclic compound **3** could be prepared through an enantioselective *Robinson* annelation, by using a modified *Hajos* and *Parrish* reaction between **6** and a conveniently substituted vinyl ketone **5**, previously introduced in our laboratory [15].

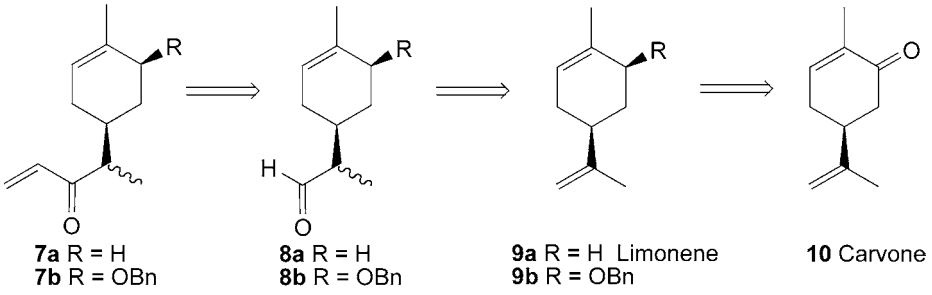
Scheme 1



To obtain compound **5b**, we selected the cyclic monoterpenes (*S*)-(+)-carvone (**10**) and (−)-(*R*)-limonene (**9a)** as suitable starting materials, since these compounds have been widely used in enantioselective synthesis of various natural products [16–20].

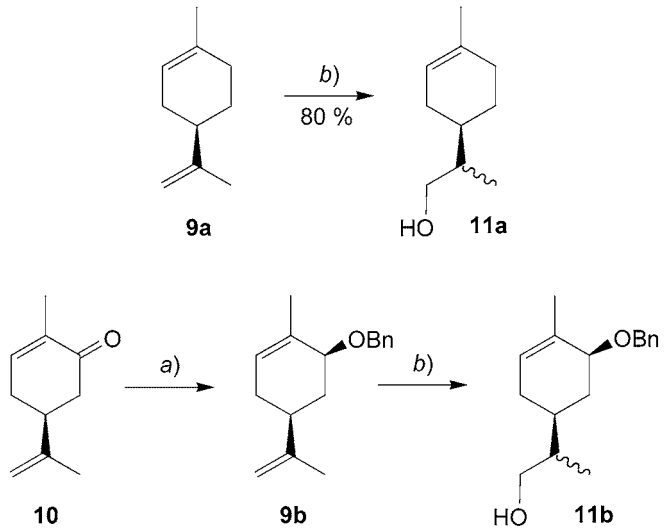
Based on a literature report [21], the synthesis of the desired vinyl ketones could be accomplished according to the retrosynthetic analysis presented in the *Scheme 2*.

Scheme 2



Results and Discussion. – To proceed with our synthetic plan, first the reduction of the C=O group of carvone (**10**) was carried out with $LiAlH_4$ in THF to furnish exclusively the β-alcohol. The origin of this stereoselective reaction may be attributed to the fact that the hydride attack occurs from the face opposite the isoprenyl chain. The resulting alcohol was protected [22] with a Bn group to yield compound **9b** in good yield (*Scheme 3*).

Scheme 3



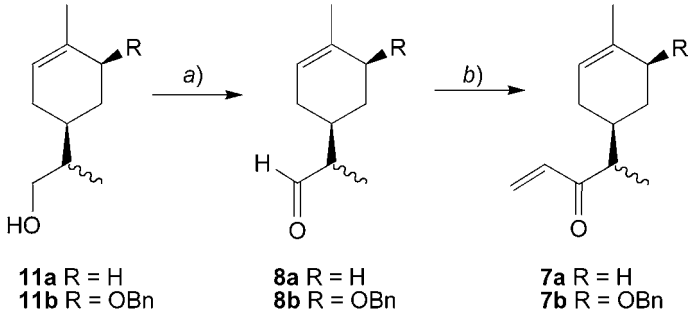
a) 1. $LiAlH_4$, Et_2O, −78°, 94%; 2. NaH, THF, Bu_4NBr, BnBr, r.t.; 87%. *b*) 1. 9-Borabicyclo[3.3.1]nonane (9-BBN), THF, 0°; 2. 1M NaOH, 30% H_2O_2; 72%.

The next step, which involved selective hydroboration/oxidation with either 9-borabicyclo[3.3.1]nonane (9-BBN) or disiamylborane, was carried out with both limonene **9a** and the protected alcohol **9b** to furnish primary alcohols **11a** and **11b**,

respectively. It was observed that both reagents selectively affect the exocyclic C=C bond to afford the alcohols in almost identical yields. To oxidize the alcohols **11a** and **11b** to the aldehydes, different oxidizing reagents and conditions were tested. After optimization, the best yields of aldehydes **8a** and **8b** were obtained by using pyridinium dichromate (PDC) in CH_2Cl_2, AcOH (catalytic), and 4-Å molecular sieves [23].

The introduction of the vinyl group with vinylmagnesium bromide in refluxing THF resulted in low yields of desired vinyl alcohols, along with alcohol **11a** as the main by-product[2]). A possible explanation of the formation of **11a** among the products implies reduction of the aldehyde. Such a reduction would be possible if a β-H of the vinyl group is concertedly transferred to the aldehyde C=O group, resulting also in formation of acetylene and the corresponding alkoxymagnesium bromide, quenched afterwards during the workup[3]). The yield of the vinyl alcohol was considerably improved when anhydrous $CeCl_3$ was added to activate the C=O group and, at the same time, to prevent the reduction reaction [25–27]. The resulting allylic alcohols were immediately oxidized to the corresponding vinyl ketones **7a** and **7b** under the same conditions as mentioned above; however, due to poor stability of these vinyl ketones, the yields could not be improved beyond 67% (*Scheme 4*).

Scheme 4



a) Pyridinium dichromate (PDC), molecular sieves (4 Å), AcOH, CH_2Cl_2; 70–85%. *b*) 1. Anh. $CeCl_3$, THF, r.t.; 2. 1M vinylmagnesium bromide, THF; 60–70%; 3. PDC, molecular sieves (4 Å), AcOH, CH_2Cl_2; 67%.

The next step involved the *Michael* addition between the synthesized vinyl ketones **7a**–**7b** and furan-dione **6** which, in turn, was prepared according to known procedures [28][29]. The reaction was performed under previously described conditions [30–32], (H_2O, AcOH (cat.), 70°). Both vinyl ketones **7a** and **7b** were submitted to *Michael*

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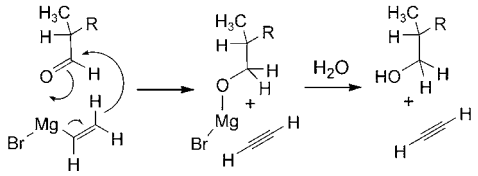
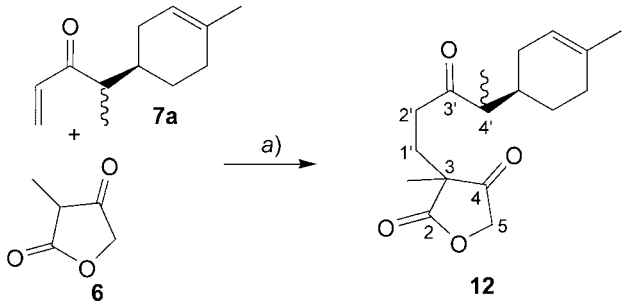
[2]) Similar behavior was recently reported for addition of vinyl *Grignard* reagents over aromatic aldehydes [24].

[3]) The proposed mechanism of aldehyde reduction by allylmagnesium bromide:



addition but, surprisingly, only **7a** reacted generating the expected adduct **12** (*Scheme 5*), whereas **7b** decomposed during the reaction. It has been reported [33] that the HOMO of the nucleophile and the LUMO of the enone is the most-favorable molecular-orbital combination that minimizes the anti-bonding interactions for addition of a nucleophile to an enone. However, a study of the vinyl ketones **7a** and **7b** at *ab initio* level of calculation (B3LYP/6-31G*) revealed that their reactivities were identical, as the conformational and the LUMO energies are similar. On the other hand, calculations have also shown that compound **7b** is considerably more polar than **7a**, and this could be a possible explanation for its different behavior. In fact, an increase in polarity would increase its susceptibility to polymerization due to the acidity of the water phase in the reaction mixture.

Scheme 5



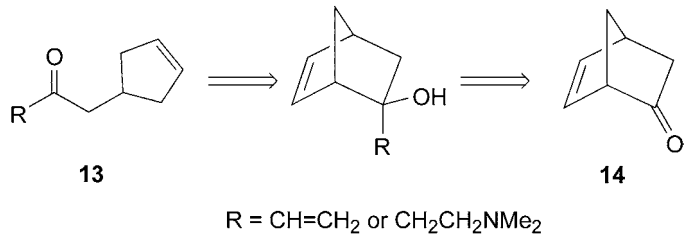
a) AcOH (cat.), H_2O, 70°; 72%.

Since vinyl ketone **7b** could not be coupled with **6**, we continued our synthesis with the adduct **12**. The cyclization was attempted under different conditions such as: L-proline, DMF [30–32]; LDA, THF, *N*,*N*′-dimethylpropyleneurea (DMPU), −78° [34]; cyclohexyl(isopropyl)amine, $BrMgCH_3$, THF, −78° [35]; $(i\text{-}Pr)_2NH$, BrMgMe, THF, −78° [36]; K_2CO_3, MeOH, −20° [37]; TsOH, benzene, reflux; and $(i\text{-}Pr)_2NH$, BrMgMe, THF, Me_3SiCl, −78° [5]. Unfortunately, all our efforts to perform the intramolecular cyclization were unsuccessful.

At this point, we presumed that compound **12** did not undergo cyclization due to the presence of the Me group in α-position to the C=O group. Careful examination of the transition states postulated for aldol cyclizations showed that, in our case, the two possible chair-like conformations presented severe steric hindrance between the $CH_2(5)$ and Me–C(4′) groups, in one conformation, and the same $CH_2(5)$ group and the cyclohexene moiety in the other. Thus, it was clear that, in order to achieve the desired ring closure, we needed to remove the Me group at C(4′). This prompted us to explore a slightly different approach involving a cyclopentenyl methyl vinyl ketone. Our retrosynthetic analysis to prepare the corresponding vinyl ketone or its precursor is presented in *Scheme 6*.

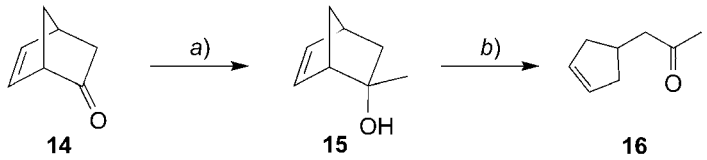
We started with the *Grignard* addition to norbornenone **14** to obtain exclusively the alcohol **15** in 99% yield, followed by an anionic fragmentation reaction of the corresponding K-alkoxide of **15** (*Scheme 7*). In this reaction, the KH-generated

Scheme 6



alkoxide was heated at 30° during 2 d to provide the methyl ketone **16** in 46% yield [38–40]. Several attempts were made to improve the yield of the last step and the results are summarized in *Table 1*.

Scheme 7



a) MeMgI, Et_2O, 0°; 99%; *b*) see *Table 1*.

Table 1. *Attempts to Improve the Yield of the Ketone* **16**

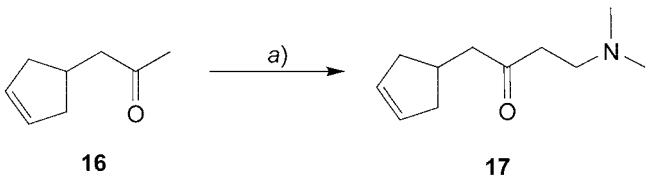
Entry	Reagents	Temp. [°]	Time [h]	Yield [%]
1	KH, HMPA	80	2.5	Decomposition
2	KH, HMPA	60	5.5	18
3	KH, HMPA	40	8	30
4	KH, HMPA	r.t.	12	52
5	KH, 18-crown-6, THF	Reflux	1.5	67

It is known that, when these reactions are conducted in low-polarity solvents, the insoluble ion pairs formed reduce the electron-donor quality of the oxido substituent that induces the rearrangement [41]. To solve this problem, *Paquette* and *Maleczka* [42] introduced the use of 18-crown-6 as a solvation agent of the anionic species, with THF as the solvent, in oxy-*Cope* anionic rearrangements. Since our anionic fragmentation reaction has the same electronic requirements, we applied this modification and increased the final yield to 67% (*Entry 5* in *Table 1*).

Finally, to generate the required vinyl ketone, we considered that the best option would be one that would allow us to generate the vinyl ketone *in situ.* After some preliminary work trying different reagents and conditions (HCHO and $(i\text{-}Pr)_2NH$ [43]; *N*-ethylanilinium trifluoroacetate with HCHO or 1,3,5-trioxane [44], methylmagnesium carbonate and 1,3,5-trioxane [45]), we finally adopted the modified *Mannich* reaction by using the *Eschenmoser* reagent [46]. A soln. of ketone **16** in THF at −78° was treated with LDA, and, after 30 min, the *Eschenmoser* salt dissolved in THF was added at the same temperature, and the mixture was allowed to warm to room

temperature. MeI was then added, and the quaternary ammonium salt was precipitated from the crude reaction mixture by dilution with Et_2O at $-20°$ (*Scheme 8*).

Scheme 8



16 **17**

a) 1. LDA, THF; 2. $CH_2{=}N^+Me_2I^-$

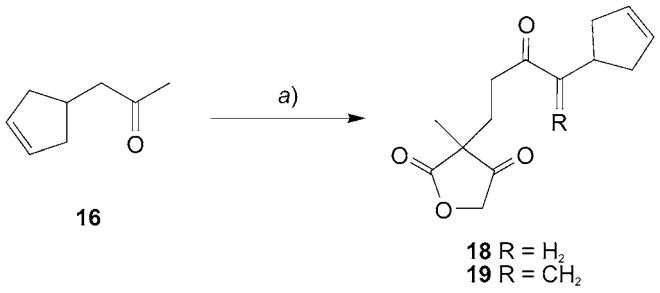
Our attempts to use the crude quaternary ammonium salt directly in a tandem *Michael* reaction with **6** under standard conditions (K_2CO_3 in anhydrous MeOH), failed. However, in a more-successful attempt, the quaternary ammonium salt was heated at 70° with furan-dione **6** in H_2O, with AcOH as catalyst. After purification, the ^{1}H-NMR spectra showed characteristic signals of the expected product together with two unexpected *singlets*, each for one H-atom, in the olefinic region at δ 6.18 and 5.96 ppm. At the same time, ^{13}C-NMR spectra showed the presence of two additional sp^2-C-atoms, one of them a quaternary C-atom (142.20 ppm) and other a terminal methylene C-atom (129.21 ppm), and an aliphatic CH_2 group was missing. All these findings are in agreement with the presence of an additional terminal C=C bond at a C-atom in the α-position to the C=O group, indicating that, during the alkylation step, 2 equiv. of *Eschenmoser* salt were incorporated, one in each of the α-positions to the C=O group, to give a diamino ketone. Afterwards, the double quaternary salt of the diamino ketone was formed, and, during the *Michael* addition, a double vinyl ketone was generated, which then reacted with **6** through the less-substituted C=C bond to give the product **19** (*Scheme 9*). To overcome this problem, we searched to find reaction conditions that would allow us to generate exclusively the kinetic enolate leading to the monoamino ketone. The best result was achieved when 1.2 equiv. of LDA was used, and the temperature was lowered to $-100°$. Compound **18** was obtained in 38% overall yield from **16**. The results are summarized in *Table 2*. Although we were able to obtain exclusively β-dimethylamino ketone **17**, we could not improve the yield over 40%.

Table 2. *Preparation of* **18** *and* **19** *from* **16**

Ratio LDA/Substrate	Temp. [°]	Global yield [%]	Ratio **18**/**19**
1.5 : 1	– 78	33	0 : 1
1 : 1	– 78	37	1.8 : 1
1.2 : 1	– 100	38	1 : 0

With furan-dione **18** in hand, we attempted the intramolecular cyclization reaction under standard conditions (TsOH in toluene at reflux) to obtain the bicyclic compound **20** in quantitative yield. The structure of **20** was fully characterized through ^{1}H- and ^{13}C-NMR spectroscopy, and by comparison with similar compounds obtained previously in our laboratory [15]. The ^{1}H-NMR spectra of **20** showed a signal for

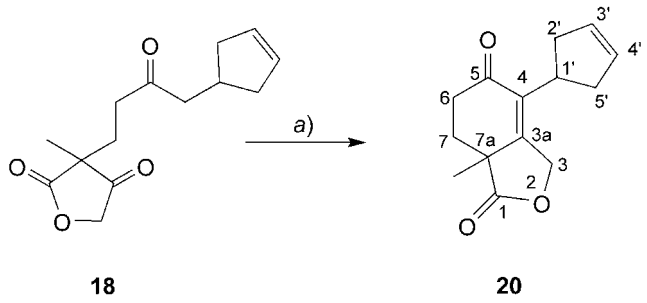
Scheme 9



a) 1. LDA, THF; 2. $CH_2{=}N^+Me_2I^-$; 3. MeI, Et_2O, 0°; 4. AcOH, H_2O, **6**, 70°.

two H-atoms at δ 5.74 ppm assigned to those of the cyclopentene ring, this time as a *multiplet*, in contrast to the *singlet* observed for the same H-atoms in the precursor. In the ^{13}C-NMR spectra, two signals, one at 130.10 and 129.22 ppm, were observed and assigned to C(3′) and C(4′) of cyclopentene ring, whereas only one signal appeared, for the same C-atoms of the precursor. An additional signal in the ^{1}H-NMR spectra (*doublet* at δ 5.00 ppm ($J = 1.4$ Hz)) assigned to H–C(3) was shifted to low-field, compared to that found in the starting material due to the C(3a)=C(4) bond proximity. The signal of the Me–C(7a) has also been observed at low field as a *singlet* at δ 1.51 ppm. Most interesting is the signal that appears as a *quintuplet* at δ 3.37 ppm, which is assigned to H–C(1′). When modeling the molecule by *ab initio* calculations, we have found two different conformations as global minima with an energy difference of 0.50 kcal/mol, which show dihedral angles of 10.9 and $-178.6°$ for C(5)–C(4)–C(1′)–H. In the more-stable one, H–C(1′) is placed almost parallel to the C=O group, having *peri*-effect with it and, in this way, deshielding its ^{1}H-NMR signal. But with this energy difference, both conformers must be in equilibrium, and, therefore, NMR spectra should show an average signal. To explain that, we finally calculated the energy barrier for the rotation of this angle, and we found 29.98 kcal/mol, high enough to justify that change of conformers is not possible.

Scheme 10



a) TsOH, toluene, reflux.

Conclusions. – Starting from natural monoterpenes, two vinyl ketones were prepared in six and four steps, respectively. On the other hand, starting from norbornenone, a vinyl-ketone precursor, the dimethylamino ketone **17**, was obtained by an anionic fragmentation reaction that was carefully studied, followed by a selective modified *Mannich* addition. All were reacted with furan-dione **6**, but the vinyl ketone **7b** did not provide the desired *Michael* product. Therefore, the two adducts **12** and **18** were submitted to an aldol reaction, but only the latter provided the expected product, even after many reagents and conditions tested on **12**. Undesirable interactions between the Me group in α-position to the C=O group and the CH_2 group of the furan-dione moiety would hinder the compound **12** to adopt the necessary conformation to form the new C–C bond. The aldol product **20** was fully characterized and will be used to continue our synthesis. In conclusion, we have achieved the formation of an interesting and properly functionalized intermediate toward the synthesis of the natural product saudin (**1**) in an efficient way.

Experimental Part

General. All solvents were dried and distilled before use. All reactions were carried out under a dry, O_2-free, N_2 atmosphere. TLC: aluminum-foil plates coated with 0.1-mm *Merck* silica gel *60 GF_{254}*. Column chromatography (CC): *Merck* silica gel *60 H*, under a low pressure of N_2, with increasing AcOEt/hexane gradients. M.p.: *Ernst Leitz* hot-stage microscope; uncorrected. IR Spectra: *Bruker FT I-25* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: at 200.1 and 50.3 MHz on a *Bruker AC-200-E* NMR spectrometer in $CDCl_3$ soln., 2D-NMR experiments were run with standard *Bruker* software. High-resolution (HR) MS: at UCR Mass Spectrometry Facility, Department of Chemistry, University of California, Riverside, USA. Elemental analyses: at *Atlantic Microlab, Inc.*, Georgia, USA. *Ab initio* calculations were performed with Gaussian 98 packages of programs [47].

*6-(Benzyloxy)-1-methyl-4-(1-methylethenyl)cyclohex-1-*ene (**9b**). To a soln. of *(S)-carvone* (**10**; 1.40 g, 9.33 mmol) in 25 ml of anh. Et_2O cooled to $-78°$, $LiAlH_4$ (380 mg, 10 mmol) was added in small portions. The mixture was stirred during 30 min at the same temp. Excess reducing reagent was carefully eliminated with wet Et_2O. The org. phase was washed with 5% NaOH and H_2O, dried (Na_2SO_4), and evaporated to yield 1.04 g (94%) of *2-methyl-5-(1-methylethenyl)cyclohex-2-en-1-ol* as colorless oil. IR (film): 3380, 3350, 3280, 3070, 2910, 2840, 1740, 1430, 1370, 1320, 1280, 1080, 1035, 1000, 970, 955, 915, 890, 855, 805, 745. ^{1}H-NMR: 1.74 (*s*, Me–C(2)); 1.74 (*s*, CH_2=CHMe); 1.9–2.4 (CH_2); 4.17 (br. *s*, H–C(1)); 4.73 (*s*, CH_2=CHMe); 5.5 (br. *s*, H–C(3)). ^{13}C-NMR: 70.60 (C(1)); 136.08 (C(2)); 20.39 (*Me*–C(2)); 123.58 (C(3)); 30.83 (C(4)); 40.32 (C(5)); 37.76 (C(6)); 18.80 (CH_2=CH*Me*); 148.77 (CH_2=*C*HMe); 108.89 (*C*H_2=CHMe); MS: 152 (24, M^+), 136 (12), 107 (20), 91 (100), 79 (46), 65 (24), 41 (32).

NaH (1.53 g, 60%, oil suspension) was washed three times with hexane in two-necked round-bottom flask under dry N_2. Later, a soln. of the alcohol (3.865 g, 25.43 mmol) in 10 ml of anh. THF was added. After 15 min, hydride was consumed, and then Bu_4NBr (200 mg) was added, followed by BnBr (3.00 ml, 25.43 mmol). The mixture was stirred under N_2 at r.t. for 1 h and then flowed on 100 ml of brine. The phases were separated, the aq. phase was extracted with Et_2O (5 × 30 ml), and the org. extracts were combined, washed with brine (2 × 25 ml), dried (Na_2SO_4), and evaporated at reduced pressure. The crude oil was purified through reduced-pressure distillation to yield 5.36 g (87%) of **9b**. Colorless oil. IR (film): 3060, 3020, 2900, 2850, 1635, 1490, 1445, 1365, 1325, 1300, 1265, 1150, 1090, 1020, 915, 885, 800, 730, 690. ^{1}H-NMR: 1.73 (*s*, Me–C(1)); 1.73 (*s*, CH_2=CH*Me*); 4.06 (br. *s*, H–C(6)); 4.51 (*d*, *J* = 11.8, 1 H, PhCH_2); 4.67 (*d*, *J* = 11.8, 1 H, PhCH_2); 4.73 (*s*, CH_2=CHMe); 5.52 (br. *s*, H–C(2)); 7.24–7.37 (*m*, 5 arom. H). ^{13}C-NMR: 78.27 (C(6)); 135.91 (C(1)); 20.90 (Me–C(1)); 125.09 (C(2)); 31.53 (C(3)); 40.32 (C(4)); 34.59 (C(5)); 19.95 (CH_2=CH-*Me*); 149.57 (CH_2=*C*HMe); 109.59 (*C*H_2=CHMe); 70.80 (Ph*C*H_2); 139.25 (arom. quat. C); 127.80 (C_o); 128.76 (C_m); 128.06 (C_p). MS: 242 (2, M^+), 231 (12), 201 (11), 169 (15), 133 (5), 107 (20), 91 (100), 78 (30), 65 (14). HR-MS: 242.1664 ($C_{17}H_{22}O^+$, M^+; calc. 242.1671).

2-(4-Methylcyclohex-3-enyl)propan-1-ol (**11a**). To the ice-cooled soln. of 9-borabicyclo[3.3.1]nonane (9-BBN; 40 ml, 0.84M, 33.6 mmol), 4.15 ml of *(R)-limonene* (**9a**; 25.7 mmol) in 10 ml of THF was dropped during

1 h. The mixture was allowed to stir at r.t. over 2 h. Subsequently, 8.3 ml of 3M NaOH and 8.3 ml of 30% P/V H_2O_2 were added dropwise alternatingly, maintaining the temp. under 10°. The resulting heterogeneous mixture was warmed to 40° and vigorously stirred for 2 h. Layers were separated, and the aqueous phase was extracted with Et_2O (3 × 30 ml), and the org. extracts were combined, dried (Na_2SO_4), and evaporated. The product was purified by distillation to yielding 3.76 g (80%) **11a**. Colorless oil. IR (film): 3410, 3350, 3290, 2920, 2905, 1455, 1385, 1160, 1050, 1035, 1020, 990, 915, 803. ^{1}H-NMR: 0.90, 0.94 (*d*, *J* = 5.0, 3 H–C(3)); 1.64 (*s*, Me–C(4′)); 3.49, 3.63 (*m*, 2 H–C(1)); 5.37 (br. *s*, H–C(3′)). ^{13}C-NMR: 66.12, 66.14 (C(1)); 39.97, 39.77 (C(2)); 13.06, 13.47 (C(3)); 35.05, 34.95 (C(1′)); 30.54, 30.41 (C(2′)*); 120.45, 120.51 (C(3′)); 133.82 (C(4′)); 23.27 (*Me*–C(4′)); 29.62, 27.49 (C(5′)*); 27.03, 25.27 (C(6′)*). MS: 152 (43, M^+), 136 (14), 121 (44), 107 (42), 94 (100), 79 (77), 67 (72), 55 (37), 41 (40).

2-[(5-(Benzyloxy)-4-methylcyclohex-3-enyl]propan-1-ol (**11b**). The same procedure for **11a** with **9b** (1.500 g, 6.20 mmol), 13 ml of anh. THF, 16.2 ml of 9-BBN (0.5M, 8.1 mmol), 2.07 ml of 3N NaOH, and 2.07 ml of 30% H_2O_2 led to **11b**. CC provided 1.17 g (72%) of **11b**. Colorless oil. IR (film): 3420, 2940, 1710, 1460, 1380, 1280, 1180, 1120, 1080, 1050, 730. ^{1}H-NMR: 0.94, 0.91 (*d*, *J* = 6.7, 3 H–C(3)); 1.75 (*s*, Me–C(4′)); 3.51 (br. *s*, 2 H–C(1)); 4.51 (br. *s*, 2 H–C(5′)); 4.50 (*d*, *J* = 11.7, 1 H, PhCH_2); 4.66 (*d*, *J* = 11.7, 1 H, PhCH_2); 4.93 (*s*, 2 H–C(6′)); 5.52 (br. *s*, H–C(3′)); 7.26–7.36 (*m*, 5 arom. H). ^{13}C-NMR: 66.30 (C(1)); 35.27 (C(2)); 13.34, 13.90 (C(3)); 40.46 (C(1′)); 30.37 (C(2′)); 125.20 (C(3′)); 135.98 (C(4′)); 19.98 (*Me*–C(4′)); 78.50 (C(5′)); 35.13 (C(6′)); 70.82 (Ph*C*H$_2$); 139.52 (arom. quat. C); 127.84 (C_o); 128.72 (C_m); 128.03 (C_p). HR-MS: 260.1784 ($C_{17}H_{24}O_2^+$, M^+; calc. 260.1776).

2-(4-Methylcyclohex-3-enyl)propanal (**8a**). In a 100-ml flask protected from light, to **11a** (2.0 g, 13 mmol) in 50 ml of anh. CH_2Cl_2, pyridinium dichromate (PDC)/Al_2O_3 (4.77 g, 38.16 mmol) was added with stirring under N_2. After 20 min, the mixture was filtered under reduced pressure over a silica-gel pad and copiously washed with CH_2Cl_2. The filtrate was dried (Na_2SO_4) and evaporated. The crude product was purified by distillation at reduced pressure to give 1.68 g (85%) of **8a**. Colorless oil. IR (film): 2930, 2885, 2950, 2685, 1710, 1450, 1430, 810. ^{1}H-NMR: 1.08 (*d*, *J* = 5, 3 H–C(3)); 1.60 (*s*, Me–C(4′)); 5.36 (br. *s*, H–C(3′)); 9.66 (*s*, H–C(1)). ^{13}C-NMR: 205.37 (C(1)); 50.61, 50.60 (C(2)); 10.16, 10.07 (C(3)); 34.15 (C(1′)); 25.26, 27.13 (C(2′)*); 119.77, 119.71 (C(3′)); 133.92 (C(4′)); 23.24 (*Me*–C(4′)); 29.61, 27.67 (C(5′)*), 29.97, 29.49 (C(6′)*). MS: 152 (2, M^+), 94 (100), 79 (69), 67 (22), 55 (15), 41 (18).

2-[5-(Benzyloxy)-4-methylcyclohex-3-enyl]propanal (**8b**). According to the same procedure for **8a**, **11b** (200 mg, 0.77 mmol) was dissolved in 11.3 ml of anh. CH_2Cl_2, and PCC/Al_2O_3 (3.85 g, 3.08 mmol) was added. CC provided 138 mg (70%) of **8b**. Yellowish oil. IR (film): 2960, 2945, 2655, 1730, 1460, 1345, 1280, 1105, 1085, 1040, 810. ^{1}H-NMR: 1.07, 1.10 (2*d*, *J* = 4.4, 4.4, 3 H–C(3)); 1.72 (*s*, *Me*–C(4′)); 4.01 (*m*, H–C(5′)); 4.45 (*d*, *J* = 25, 1 H, PhCH_2); 4.65 (*d*, *J* = 25, 1 H, PhCH_2); 5.49 (br. *s*, H–C(3′)); 7.26–7.36 (*m*, 5 arom. H); 9.67 (*d*, 2 H–C(1)). ^{13}C-NMR: 206.2 (C(1)); 50.81, 50.53 (C(2)); 11.26, 11.47 (C(3)); 31.25 (C(1′)); 26.36, 27.43 (C(2′)*); 120.17, 120.11 (C(3′)); 134.02 (C(4′)); 22.64 (*Me*–C(4′)); 24.61, 23.67 (C(5′)*), 28.67, 25.49 (C(6′)*), 72.82 (Ph*C*H$_2$); 138.92 (arom. quat. C); 125.94 (C_o); 124.65 (C_m); 127.63 (C_p). HR-MS: 272.1771 ($C_{18}H_{24}O_2^+$, M^+; calc. 272.1776).

4-(4-Methylcyclohex-3-enyl)pent-1-en-3-one (**7a**). *Method A* (without anh. $CeCl_3$). In two-necked round-bottom flask with a reflux condenser, a soln. of **8a** (95 mg, 0.37 mmol) in 10 ml of anh. THF was cooled to 0°. Then, 1M vinylmagnesium bromide in THF (0.5 ml, 0.5 mmol) was added. The mixture was heated at reflux over 2 h. After cooling to r.t., 10 ml of 3M NaOH was added, and the phases were separated. The aq. phase was extracted with Et_2O (4 × 25 ml), and the org. extracts were combined and washed with H_2O, dried (Na_2SO_4), and evaporated. After purification by CC 68.6 mg (60%) of vinyl alcohol as yellowish oil and 19.8 mg (15%) of **11a** were obtained.

Method B (with $CeCl_3$). To a soln. of **8a** (300 mg, 2.03 mmol) in 10 ml of anh. THF was added anh. $CeCl_3$ (500.4 mg), and the mixture was stirred for 20 min. Thereafter, vinylmagnesium bromide (2.24 ml of 1M THF soln; 2.24 mmol) was added at r.t. and the mixture was allowed to react over 1 h. Then, 10 ml of 10% AcOH was added, and the soln. was extracted with Et_2O (3 × 15 ml). Org. extracts were washed with brine and sat. $NaHCO_3$, dried ($MgSO_4$), and evaporated: 248 mg of colorless oil were obtained (70% yield). The crude product was oxidized to the vinyl ketone immediately without purification. A fraction purified by CC showed the following ^{1}H-NMR signals: 0.90 (*d*, *J* = 5, 3 H–C(5)); 1.64 (*s*, Me–C(4′)); 4.2 (*m*, 2 H–C(3)); 5.15 (br. *s*, 2 H–C(1)); 5.4 (br. *s*, H–(3′)); 5.8 (*m*, H–C(2)).

To a soln. of the alcohol (270 mg, 1.6 mmol) in 10 ml of CH_2Cl_2, protected against light, PDC (715 mg, 1.92 mmol), 1.2 g of molecular sieves (4 Å), and finally 25 µl of AcOH were added simultaneously. The mixture was allowed to stir over 30 min, and then filtered through *Celite* and silica gel pad with CH_2Cl_2. Solvent was evaporated, and the product was purified by distillation at reduced pressure to give 178 mg (67%) of **7a**. IR

(film): 2980, 2905, 2705, 1680, 1600, 1380, 1250, 1100, 1020, 970. ^{1}H-NMR: 1.04 (*d*, *J* = 5.0, 3 H=C(5)); 1.62 (*s*, Me−C(4′)); 2.70 (*m*, H−C(1′)); 2.70 (*m*, H−C(4)); 5.40 (br. *s*, 1 H−C(5′)); 5.35 (br. *s*, 1 H−C(5′)); 5.76 (*dd*, *J* = 2.1, 10.2, H−C(2)); 6.46 (*ddd*, *J* = 17.6, 10.2, 2.89, H−C(1)). ^{13}C-NMR: 135.45 (C(1)); 127.83 (C(2)); 204.24 (C(3)); 48.47, 47.64 (C(4)); 13.24 (C(5)); 35.72 (C(1′)); 30.10 (C(2′)*), 119.87 (C(3′)); 133.86 (C(4′)); 23.26 (*Me*−C(4′)); 28.21 (C(5′)*), 27.79 (C(6′)*).

4-[5-(Benzyloxy)-4-methylcyclohex-3-enyl]pent-1-en-3-one (**7b**). *Method B* was applied. Aldehyde **8b** (260 mg, 1.0 mmol) was dissolved in 10 ml of anh. THF, and 250 mg of anh. $CeCl_3$ and vinylmagnesium bromide (1M in THF, 1.12 ml, 1.12 mmol) were added. 195 mg (68%) of a colorless oil was obtained. A fraction purified by CC showed the following ^{1}H-NMR signals: 0.94 (*d*, *J* = 5, 3 H−C(5)); 1.75 (*s*, Me−C(4′)); 3.80 (*m*, 2 H−C(3)); 4.72, 4.5 (*d*, PhCH_2); 5.15 (br. *s*, 2 H−C(1)); 5.5 (br. *s*, H−C(3′)); 5.8 (*m*, H−C(2)); 7.37–7.34 (*m*, 5 arom. H).

The same preparation technique for **7a** was applied. Vinyl alcohol (440 mg, 1.6 mmol) was dissolved in 10 ml of CH_2Cl_2 and PDC (715 mg, 1.92 mmol), 1.2 mg of molecular sieves (4 Å), and 25 µl of AcOH were used: 284 mg (69%) of **7b** were obtained. IR (film): 3120, 2960, 2925, 2735, 1660, 1580, 1380, 1260, 1050, 1020, 970, 880. ^{1}H-NMR: 1.06 (*d*, *J* = 4.8, 3 H−C(5)); 1.64 (*s*, Me−C(4′)); 2.70 (*m*, H−C(1′)); 2.70 (*m*, H−C(4)); 4.51 (*d*, *J* = 11.8, 1 H, PhCH_2); 4.67 (*d*, *J* = 11.8, 1 H, PhCH_2); 5.34 (br. *s*, H−C(3′)); 5.86 (*dd*, *J* = 2.6, 10.7, H−(2)); 6.56 (*ddd*, *J* = 15.6, 11.2, 3.09, 2 H−C(1)); 7.24–7.37 (*m*, 5 arom. H). ^{13}C-NMR: 134.75 (C(1)); 126.83 (C(2)); 203.74 (C(3)); 47.47, 46.63 (C(4)); 13.27 (C(5)); 36.42 (C(1′)); 31.20 (C(2′)*), 117.24 (C(3′)); 134.86 (C(4′)); 22.26 (Me−C(4′)); 29.01 (C(5′)*); 28.89 (C(6′)*); 72.80 (PhCH_2); 136.25 (arom. quat. C); 126.70 (C_o); 129.06 (C_m); 127.96 (C_p).

3-Methyl-3-[4-(4-methylcyclohex-3-enyl)-3-oxopentyl]furan-2,4-dione (**12**). A mixture of **7a** (160 mg, 0.95 mmol) and *2,3,4,5-tetrahydro-3-methylfuran-2,4-dione* (**6**; 75 mg, 0.64 mmol) was dissolved in 10 ml of dist. H_2O, and 10 µl of AcOH was added. Under protection against light, the mixture was heated at 70° during 3 h. Thereafter, the mixture was saturated with NaCl and extracted with CH_2Cl_2 (3 × 20 ml). The combined org. phases were dried (Na_2SO_4), and solvent was evaporated to provide 150 mg of a yellow oil. Purification by CC yielded 130 mg (72%) of **12**. Yellowish oil. IR (film): 2960, 2940, 1800, 1760, 1440, 1370, 1340, 1310, 1270, 1130, 1075, 1050, 950, 920, 850, 805, 760, 740, 705. ^{1}H-NMR: 0.99, 1.02 (2*d*, *J* = 4.7, 5.2, 3 H−C(5′)); 1.33 (*s*, Me−C(3)); 1.63 (*s*, Me−C(4″)); 1.90 (*m*, 2 H−C(5″)); 1.90 (*m*, 2 H−C(2″)); 2.36 (*m*, H−C(4′)); 2.55 (*m*, 2 H−C(2′)); 4.71 (*d*, *J* = 17, 1 H−C(5)); 4.86 (*d*, *J* = 17, 1 H−C(5)); 5.35 (br. *s*, H−C(3″)). ^{13}C-NMR: 72.14 (C(1)); 208.76 (C(2)); 46.46 (C(3)); 20.50, 20.60 (*Me*−C(3)); 176.75 (C(4)); 35.50 (C(1′)*); 35.55 (C(2′)); 213.87 (C(3′)); 35.6 (C(4′)); 13.01, 13.09 (C(5′)); 31.52, 30.66 (C(1″)); 28.18, 20.12 (C(2″)); 119.69 (C(3″)); 133.83 (C(4″)); 23.23 (*Me*−C(4″)); 30.04, 29.88 (C(5″)); 27.73, 28.01 (C(6″)). HR-MS: 292.1678 ($C_{17}H_{24}O_4^+$, M^+; calc. 292.1675).

2-Methylbicyclo[2.2.1]hept-5-en-2-ol (**15**). In a two-necked round-bottom flask, with a reflux refrigerant and a pressurized aggregate ampoule, to 83.4 mmol of MeMgBr dissolved in 30 ml of anh. Et_2O a soln. of **14** (3.83 g, 35.42 mmol) in 20 ml of anh. Et_2O was introduced in the ampoule. The flask was cooled to 0°, and **14** was dropped to the *Grignard* reagent, and the mixture was refluxed over 30 min. After cooling, the mixture was added in 50 ml of sat. NH_4Cl. The phases were separated, and the aq. phase was extracted with Et_2O (5 × 20 ml), and the org. extracts were pooled, dried (Na_2SO_4), and evaporated to yield 4.35 g (99%) of **15** as a yellowish liquid. ^{1}H- and ^{13}C-NMR, IR, and mass spectra are identical with those reported in [37].

1-(Cyclopent-3-enyl)propan-2-one (**16**). *Method 1*. In a two-necked round-bottom flask KH (40% oil suspension; 3.88 g, 38.82 mmol) was carefully washed with hexane. A reflux condenser was incorporated, and KH was suspended in 70 ml of anh. hexamethylphosphoramide (HMPA). Simultaneously, **15** (4.4 g, 35.3 mmol) dissolved in 17 ml of anh. HMPA was added dropwise during 5 min to the cooled suspension of KH. The reaction was allowed to proceed for 15 min at this temp., and then the mixture was heated at 45° overnight. After cooling, the mixture was carefully poured into 80 ml of sat. NH_4Cl, and then extracted with Et_2O (3 × 40 ml). Org. extracts were pooled and washed with brine, dried (Na_2SO_4), and evaporated by distillation at normal pressure to yield the crude product. This crude material was purified by CC (silica gel; CH_2Cl_2). The solvent was evaporated at normal pressure, and the residue was distilled to give 1.98 g of **16** as a colorless liquid.

Method 2. In a two-necked round-bottom flask, 20% oil suspension KH (965 mg, 4.82 mmol) was washed with hexane. Reflux condenser was incorporated, and KH was suspended in 20 ml of anh. THF. Then, anh. HMPA (0.84 ml, 4.84 mmol) was added, and the soln. was cooled to 0°. A soln. of **15** (300 mg, 2.42 mmol) in 4 ml of anh. THF was added dropwise to the KH suspension under stirring. The reaction was continued for 15 min at r.t., and then 18-crown-6 (1.27 g, 4.84 mmol) in 4 ml of THF was added to the mixture. The resulting mixture was heated under reflux for 1 h. After cooling to −78°, 15 ml of sat. NH_4Cl was carefully added. The mixture was warmed up to r.t. and the same workup as in *Method 1* led to 205 mg of **16**. IR ($CHCl_3$): 3025, 2965, 1720, 1445, 1320, 1380, 1355, 1275, 1250, 1190, 1180, 1105, 970, 845, 755. ^{1}H-NMR: 1.93 (*dd*, *J* = 12.4, 4.0, 2 H−C(2)); 2.14 (*s*, 3 H−C(3)); 2.53 (*m*, H−C(1′)); 2.62 (*m*, 2 H−C(2), 2 H−C(5′)); 5.86 (*s*, H−C(3′), H−C(4′)). ^{13}C-NMR:

29.92 (C(1)); 208.60 (C(2)); 50.57 (C(3)); 32.44 (C(1′)); 38.67 (C(2′), C(5′)); 129.41 (C(3′), C(4′)). MS: 124 (22, M^+), 82 (46), 44 (100).

3-[4-(Cyclopent-3-enyl)-3-oxobutyl]-3-methylfuran-2,4-dione (**18**). To a soln. of $(i\text{-}Pr)_2NH$ (1.02 ml, 7.9 mmol) in 8 ml of anh. THF, LiBu (5.7 ml, 1M in hexane; 6.8 mmol) was carefully added at r.t. This soln. was stirred at this temp. over 10 min and then cooled to $-100°$. Ketone **16** (700 mg, 5.64 mmol) in 10 ml anh. THF was added dropwise under stirring over 30 min, and the temperature was kept at $-100°$. In a separate flask, a suspension of *Eschenmoser* salt (2.1 g, 11.28 mmol) in 10 ml of anh. THF was prepared and cooled to $-100°$. With a canula, the enolate was transferred to *Eschenmoser* suspension, and the mixture was left to react for 35 min. Thereafter, the mixture was warmed to r.t., and the reaction was quenched with brine. The mixture was extracted with Et_2O (3×30), then the Et_2O phases were pooled and extracted with 6N HCl (3×15 ml). Acidic extracts were neutralized with 1M NaOH and extracted again with Et_2O (4×10 ml), dried (Na_2SO_4), and evaporated to provide 870 mg of crude product. Amino ketone was dissolved in 2 ml of MeI, and the mixture was cooled to $-20°$. Et_2O was added dropwise to facilitate the precipitation of ammonium salt, and then the mixture was left to react at $-20°$ for an additional h. The precipitate was separated and washed with cold Et_2O twice and dried under vacuum. The solid was dissolved in 10 ml of H_2O; **6** (428 mg, 3.76 mmol) and AcOH (50 µl) were added. The soln. was kept at 70° over 3 h. The aq. soln. was saturated with NaCl and extracted with CH_2Cl_2 (3×15 ml). Org. extracts were combined, dried (Na_2SO_4), and evaporated. Purification by CC provided 536 mg (38% from **16**) of **18**. Yellow oil. IR (film): 2935, 1820, 1755, 1460, 1325, 110, 1270, 1100, 1065, 985, 855, 755, 730. ^{1}H-NMR: 1.31 (*s*, Me–C(8)); 2.47 (*m*, 2 H–C(2′), 2 H–C(4′)); 4.59 (*d*, $J=12$, 1 H–C(5)); 4.75 (*d*, $J=12$, 1 H–C(5)); 5.62 (*s*, H–C(3″), H–C(4″)). ^{13}C-NMR: 176.65 (C(2)); 46.40 (C(3)); 20.22 (Me–C(3)); 209.36 (C(4)); 72.09 (C(5)); 28.15 (C(1′)); 36.52 (C(2′)); 208.86 (C(3′)); 49.27 (C(4′)); 32.22 (C(1″)); 38.61 (C(2″), C(5″)); 129.36 (C(3″), C(4″)). MS: 250 (10, M^+), 184 (13), 169 (10), 115 (52), 79 (13), 71 (47), 66 (100), 55 (35), 41 (26).

With LDA/**16** 1:1, *3-[4-(cyclopent-3-enyl)-3-oxopent-4-enyl]-3-methylfuran-2,4-dione* **19** was isolated. IR (film): 2945, 1820, 1755, 1710, 1520, 1495, 1425, 1310, 1255, 1105, 1075, 950, 885, 785, 715. ^{1}H-NMR 1.32 (*s*, Me–C(3)); 2.47 (*m*, 2 H–C(1′), 2 H–C(2′)); 4.56 (*d*, $J=16.5$, 1 H–C(5)); 4.78 (*d*, $J=16.5$, 1 H–C(5)); 5.65 (*s*, H–C(3″), H–C(4″)); 5.96 (*s*, 1 H, $=CH_2$); 6.15 (*s*, 1 H, $=CH_2$). ^{13}C-NMR: 175.45 (C(2)); 47.04 (C(3)); 20.34 (*Me*–C(3)); 208.09 (C(4)); 72.34 (C(5)); 37.01, 28.15 (C(1′)); 38.70 (C(2′)); 201.84 (C(3′)); 129.21 (C(5′)); 142.2 (C(4′)); 32.56 (C(1″)); 38.71 (C(2″), C(5″)); 129.47 (C(3″), C(4″)).

*4-(Cyclopent-3-enyl)-7,7a-dihydro-7a-methyl-3*H,*6*H*-[2]benzofuran-1,5-dione* (**20**). A soln. of 230 mg of **18** in toluene (5 ml) and 5 mg of TsOH was heated at reflux for 2 h. The soln. was diluted with AcOEt, washed with brine and H_2O, dried ($MgSO_4$), and evaporated. Purification by CC provided 213 mg (100%) of **20**. White crystalline solid. M.p. 121–122.5° (Et_2O) IR (film): 2940, 2870, 1785, 1740, 1680, 1460, 1365, 1275, 1190, 1120, 1010, 960, 745, 710. ^{1}H-NMR: 1.51 (*s*, Me–C(7a)); 3.37 (*m*, H–C(1′)); 5.00 (*d*, $J=1.4$, 2 H–C(3)); 5.74 (*t*, $J=2.5$, H–C(3′), H–C(4′)). ^{13}C-NMR: 178.13 (C(1)); 66.94 (C(3)); 154.52 (C(3a)); 137.41 (C(4)); 195.85 (C(5)); 32.95 (C(6)); 29.02 (C(7)); 41.36 (C(7a)); 21.36 (*Me*–C(7a); 33.20 (C(1′)); 38.98 (C(2′)); 129.12 (C(3′)); 130.10 (C(4′)) 39.68 (C(5′)). MS: 232 (33, M^+), 217 (27), 204 (100), 175 (40), 147 (27), 131 (30), 115 (37), 91 (73), 77 (80), 65 (40), 41 (50). HR-MS: 233.1170 ($C_{14}H_{17}O_3^+$, $[M+H]^+$; calc. 233.1178).

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