Letters in Organic Chemistry, 2017, *14*, 181-185

RESEARCH ARTICLE

A Short Route to the Ester (±) HomoSarkomycin *via* Johnson-Claisen Rearrangement

M'hamed Saied[1], Rafik Gatri[1,2,*], Abdullah Sulaiman Al-Ayed[2], Youssef Arfaoui[3] and Mohamed Moncef El Gaied[4]

[1]*Département de Chimie, Faculté des Sciences de Tunis Laboratoire de Synthèse Organique et Hétérocyclique, Campus Universitaire, Université Tunis El Manar 2, 2092 Tunis, Tunisia;* [2]*Chemistry Department, College of Science and Arts at Ar Rass, Qassim University, Burayadah 51477, Saudi Arabia;* [3]*Unité Physico Chimie des Matériaux Condensés - UR11ES19 , Faculté des Sciences de Tunis, Campus Universitaire, Université Tunis El Manar 2, 2092 Tunis, Tunisia*

ARTICLE HISTORY

Received: October 07, 2016
Revised: November 29, 2016
Accepted: December 20, 2016

DOI:
10.2174/1570178614666161230123513

Abstract: ***Background***: α-Methylene cycloalkanones are considered of interest because of their biological activity. Herein, in this paper the synthesis of (±) HomoSarkomycine Esters was described and characterized.

Methods: Using Bylis-Hillman adducts, triethlorthoacetate and propanoic acid, (±) HomoSarkomycine Esters could be synthesized by smoothly Johnson-Claisen rearrangement.

Results: A small library of target compounds was prepared under optimized reaction conditions in moderate yields. The reaction mechanism and the DFT study have been investigated.

Conclusion: This methodology provides ready access to 2-hydroxymethyl-2-cyclopentenone **1a** which can be served as the raw materials of the synthesis of (±) HomoSarkomycine Ester.

Keywords: Baylis-Hillman reaction, homosarkomycine, 2-hydroxymethylcyclopentenone, Johnson-Claisen rearrangement.

1. INTRODUCTION

α-Methylene cycloalkanones [1-12] (Fig. **1**) are considered as versatile intermediates to natural products [13-15] and are of current interest because of their anti-tumor activity [16, 17]. Some examples of active compounds are presented below [18-20]. Smith III, A.B. *et al.* prepared (±)HomoSarkomycin Ester 2a by the Johnson-Claisen rearrangement of the ketal of 1a, after hydrolysis of the ester and ketal functionalities [16].

In continuation of our interest in the synthesis of biological compounds [21-23], we established an efficient synthesis of the (±) HomoSarkomycin Ester 2a *via* a Johnson-Claisen rearrangement using the Baylis-Hillman adduct 1a (Scheme **1**), that was prepared (in our laboratory) [24] in one step from 2-cyclopentenone in high yield and in relatively high scale.

2. RESULTS AND DISCUSSIONS

The Baylis-Hillman reaction produces highly functionalized adducts such as **1a** [24] which may serve as the starting materials for the synthesis of useful targets. We envisaged that the Johnson-Claisen rearrangement [25] would be a powerful and practical route to the (±) HomoSarkomycine Ester **2a** (Scheme **1**).

The reaction between 2-hydroxymethyl-2-cyclopentenone (**1a**) [24] and triethyl orthoacetate in the presence of propanoic acid at 150°C leads to (±) HomoSarkomycine Ester (**2a**) *via* a [3,3] sigma-tropic rearrangement (Scheme **1**, Table **1**).

In a second step, we studied if this Johnson-Claisen rearrangement can be generalized in order to access to α-alkylidene-β-methylethoxycarbonyl cyclopentanones **2b-d** [24] (Scheme **2**, Table **1**). The corresponding α-alkylidene cyclopentanone adducts were obtained in moderate yield in all the cases.

It should be noted that the reaction with **1e** results in the esterification product **2e** instead of the rearrangement (Scheme **3**).

A plausible mechanism for the formation of compounds **2a-d** and **2e** is depicted in Scheme **4**.

These mechanisms are supported by the following calculations.

*Address correspondence to this author at the Department of Chemistry, College of Sciences and Arts at Ar Rass, Qassim University, P.O. Box: 51477, Buraydah, Saudi Arabia; Tel: 00966563680500;
E-mail: rafik.gatri@gmail.com

1875-6255/17 $58.00+.00

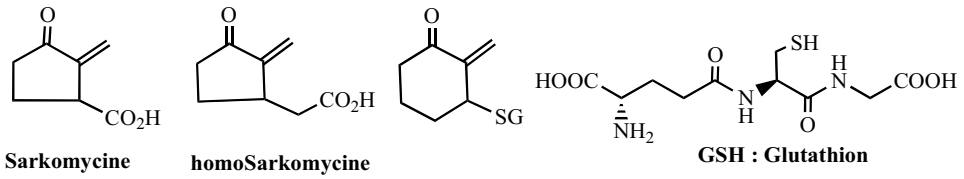
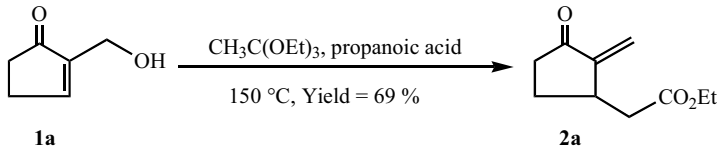
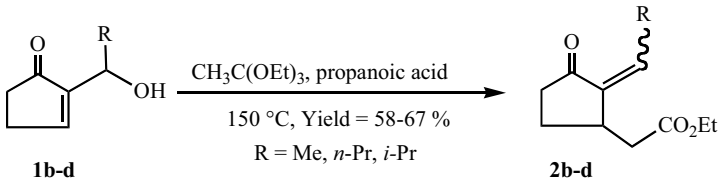


Fig. (1). Structures of α-Methylene cycloalkanones.



Scheme (1). Synthesis of (±) HomoSarkomycin Ester **2a**.

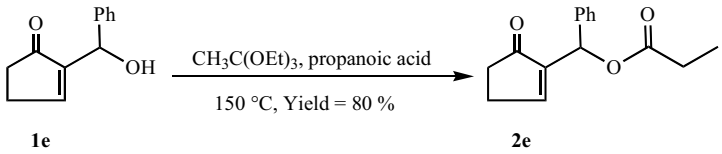


Scheme (2). Synthesis of α-alkylidene-β-methylethoxycarbonyl cyclopentanones **2b-d**.

Table 1. Synthesis of 2a-d from 1a-d with Johnson-Claisen rearrangement.

2	a	b	c	d
R	H	Me	n-Pr	i-Pr
Time	4 h	4 h	5h 30 mn	6h
*Z/E**	-	20/80	30/70	10/90
Yield (%)	70	60	58	64

* The proportion is calculated from the ^{1}H NMR.



Scheme (3). Synthesis of 2-(1-Phenyl-propanoyloxyméthyl)cyclopent-2-en-1-one **2e**.

Computational Details

The geometries of the CH_3-$C(OC_2H_5)_3$, CH_3CH_2-COOH, 2-(1-hydroxyethyl)cyclopentenone **1b** and 2-(phenyl-hydroxymethyl)cyclopentenone **1e** are optimized by Density Functional Theory calculations applying the functional B3LYP and the 6-31G (d) basis set and using the GAUSSIAN 09 program [26-28]. To characterize the reactivity, we used Fukui function, defined as the differential change in electron density due to an infinitesimal change in the number of electrons. The condensed Fukui functions of an atom, say k, in a molecule with N electrons are defined for nucleophilic and electrophilic attack, respectively as:

$$f_k^+ = q_k(N+1) - q_k(N)$$

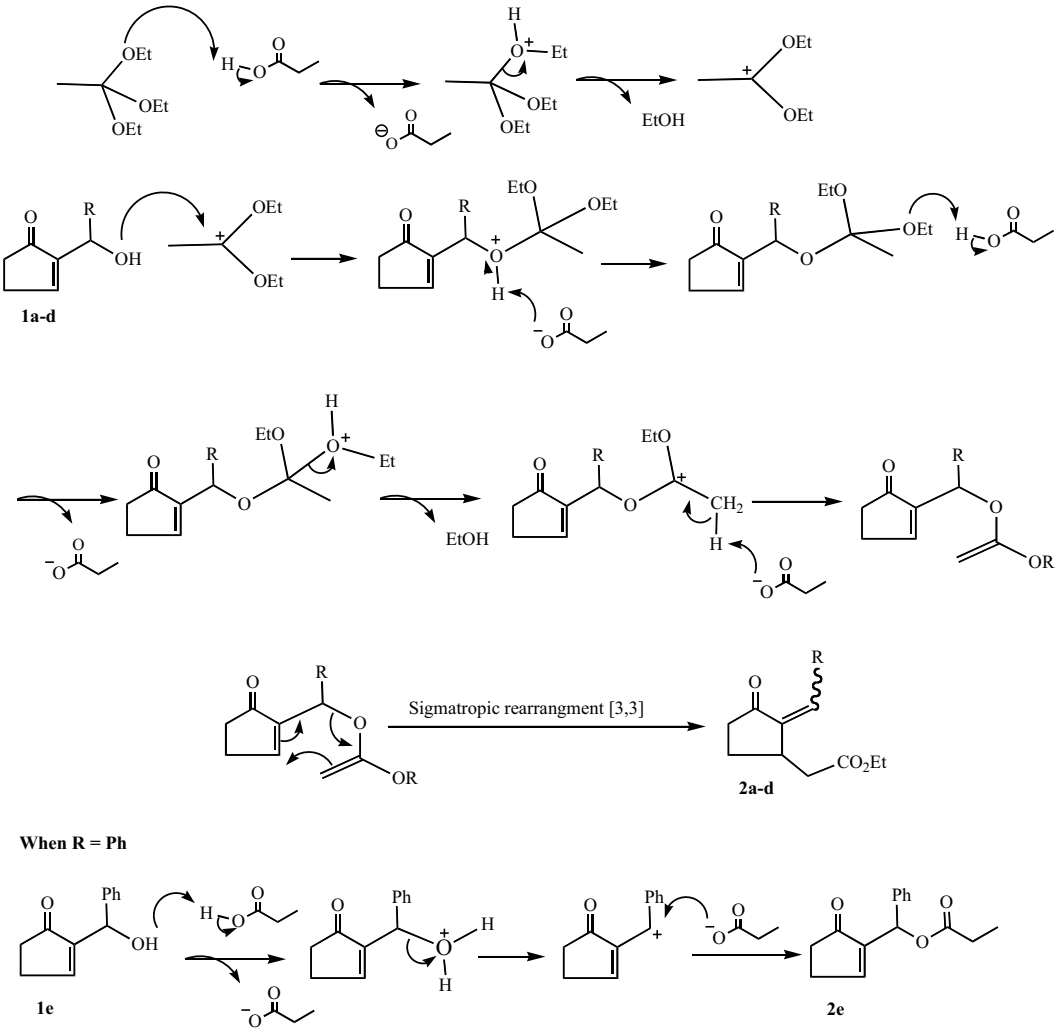
$$f_k^- = q_k(N) - q_k(N-1)$$

Where q_k is the electronic population of atom k in a molecule. The corresponding local softness parameters can be defined as [29-31]:

$$S_k^+ = S f_k^+ \quad ; \quad S_k^- = S f_k^-$$

The global softness is defined as $S = \frac{1}{2\eta}$.

The hardness is given by $\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$.



Scheme (4). A plausible mechanism for the formation of compounds **2a-d** and **2e**.

Table 2. Calculated local reactivity properties of the selected molecules using BLYP/6-31g(d) method for NBO derived charges.

Entry	O_1	O_2	C_3	H_4
$f_{\bar{k}}$	0.177	0.046		
$f_{k}^{\pm}$			0.423	0.116
E_{LUMO} - E_{HOMO}	0.19458	0.17922	0.28787	0.27589
η	0.09729	0.08961	0.14393	0.13794
S	5.1390	5.5797	3.47380	3.6250
$S_{\bar{k}}$	0.9096	0.2567		
$S_{k}^{\pm}$			1.4660	0.4205

Results of local reactivity properties of the selected molecules are summarized in Table **2** and Fig. (**2**).

In this study, we have presented the reactivity parameters, the local softness $S_{k}^{\pm}$ and $S_{\bar{k}}$ of the corresponding propanoic acid, orthoester and the two Baylis-Hillman adducts (**1b** and **1e**) and the most reactive sites for nucleophilic and electrophilic attack were derived. If we match the $S_{k}^{\pm}$ values of the C_3 and H_4 atoms of the orthoester and propanoic acid, respectively with $S_{\bar{k}}$ values of the oxygen O_1 and O_2 in the OH group of the Bayliss-Hillman adducts 1b and 1e, respectively, one finds clearly that the $S_{\bar{k}}$ of the O_1 atom match better with the $S_{k}^{\pm}$ values of the of C_3 atom, whereas the $S_{\bar{k}}$

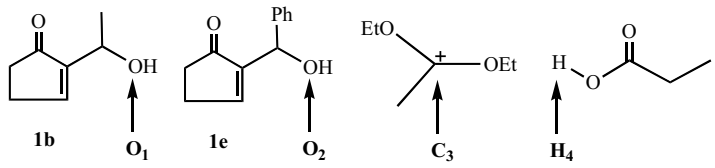


Fig. (2). The 4 atoms O_1, O_2, C_3 and H_4.

of the O_2 atom match better with the H_4 atom (Fig. **3**). Thus the local HSAB principle also predicts the reaction in accordance with the experimentally proved evidence.

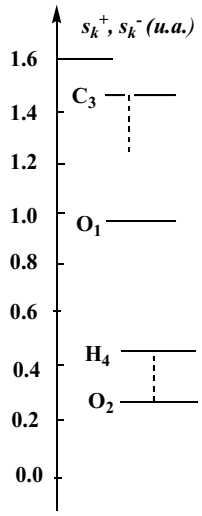


Fig. (3). Local softness for the 4 atoms O_1, O_2, C_3 and H_4.

3. EXPERIMENTAL

Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-300 MHz spectrometer as a solution in deuterochloroform. Infrared (IR) spectra were recorded on a Perkin–Elmer Spectrum (FT_IR specter Pargon 1000 PC). The products are dosed on an automatic analyzer type SCA-CHN with detector of thermal conductivity-meter: catharometer (INRAP, Tunisia). The plates used for thin-layer chromatography (TLC) were E. Merck silica gel 60F254 (0.25 mm thickness) precoated on aluminum plates, and they were visualized under both long (365 nm) and short (254 nm) UV light. All compounds were purified by column chromatography (Silica gel 60, 70-230 mesh ASTM). Mass Spectra (MS) were carried out on a Hewlett-Packard 5890 (70 ev) by the staff of Medicine Faculty of Monastir, Tunisia, under electronic impact (EI) using NH_3 as the carrier gas.

3.1. Representative Procedure for the Synthesis of 2a-e

A 25 mL round bottomed flask was charged with 2-hydroxymethyl-2-cyclopentenone **1a** (3 mmol, 336 mg), triethylorthoacetate (3.6 mmol, 583 mg) and propionic acid (3 mmol, 222 mg). The resulting mixture was stirred at reflux for 4 hours. When the reaction was completed, the mixture was basified by 5 mL of saturated solution of $NaHCO_3$ and extracted with 40 mL of ethyl acetate. After the usual work, the crude product was purified by column chromatography on silica gel using Diethyl ether/Petroleum ether (1:9) as eluent, gave pure **2a** in 70% yield.

3.1.1. 3-Ethoxycarbonylmethyl-2-methylenecyclopentan-1-one (2a)

IR ($CHCl_3$) cm^{-1}: 1727 (C=O, ester), 1708 (C=O, ketone). ^{1}H NMR (300 MHz, $CDCl_3$): 6.05-5.28 (AA', J = 2.9 Hz, 2H), 4.19 (q, J = 6.9 Hz, 2H,), 3.20 (m, 1H), 2.73-2.66 (d, 1H), 2.47-2.17 (m, 4H), 1.58 (m, 1H), 1.30 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 206.1, 171.8, 147.6, 117.1, 60.6, 38.9; 37.5, 36.9, 26.5, 14.2. MS (*m/z*): 41(39), 53 (88), 67 (71), 79 (64), 98 (73), 108 (100), 125 (46), 137 (57), 154 (86), 182 (M^+; 65). Elemental Analysis for $C_{10}H_{14}O_3$ calcld: C, 65.91 H, 7.74 found: C, 65.98; H, 7.86.

3.1.2. 3-Ethoxycarbonylmethyl-2-ethylidenecyclopentan-1-one (2b)

IR ($CHCl_3$) cm^{-1}: 1715 (C=O, ester), 1698 (C=O, ketone). ^{1}H NMR (300 MHz, $CDCl_3$): 6.66 et 6.03 (q, J = 2.9 Hz, 1H), 4.17 (q, J = 6.9 Hz, 2H), 3.48 (m, 1H), 2.38-2.05 (m, 6H), 1.88 (d, J = 2.9 Hz, 3H), 1.27 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 206.0, 171.5, 147.1, 125.2, 60.4, 38.6, 37.3, 35.9, 26.4, 24.3, 14.1. MS (*m/z*): 41 (27), 67 (21), 79 (43), 109 (100), 123 (39), 151 (19) 196 (M^+; 65). Elemental Analysis for $C_{11}H_{16}O_3$ calcld: C, 67.32; H, 8.22 found: C, 67.40; H, 8.33.

3.1.3. 3-Ethoxycarbonylmethyl-2-butylidenecyclopentan-1-one (2c)

IR ($CHCl_3$) cm^{-1}: 1717 (C=O, ester), 1695 (C=O, ketone). ^{1}H NMR (300 MHz, $CDCl_3$): 6.64 and 5.56 (t, J = 2.9 Hz, 1H), 4.22 (q, J = 6.9 Hz, 2H), 2.58 (m, 4H), 2.44-2.34 (m, 4H), 2.05-1.71 (m, 4H), 1.25 (m, 2H), 1.15 (t, J = 6.9 Hz, 3H), 0.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 207.3, 173.6, 158.3, 145.6, 69.2, 35.3, 35.1, 29.7, 27.7, 26.5, 18.5, 13.7, 9.2. MS (m/z): 41 (13), 55 (15), 67 (18), 79 (21), 95 (21), 107 (11), 121 (11), 137 (100), 224 (M^+; 29). Elemental Analysis for $C_{13}H_{20}O_3$ calcd: C, 69.61; H, 8.99, found: C, 69.55; H, 9.12.

3.1.4. 3-Ethoxycarbonylmethyl-2-(2-methylpropylidene) cyclopentan-1-one (2d)

IR ($CHCl_3$) cm^{-1}: 1722 (C=O, ester), 1703 (C=O, ketone). ^{1}H NMR (300 MHz, $CDCl_3$): 6.41 (d, J = 2.9 Hz, 1H), 4.17 (q, J = 6.9 Hz, 2H), 3.74 (m, 1H), 2.44-1.85 (m, 7H), 1.25 (t, J = 6.9 Hz, 3H), 1.04 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 207.0, 171.8, 144.2, 137.4, 60.7, 39.4, 35.8, 34.8, 29.7, 28.7 25.2, 22.1, 14.2. MS (m/z): 41 (13), 55 (14), 67 (17), 79 (23) 95 (18), 109 (16), 121 (10), 137 (100), 179 (8), 224 (M^+; 30). Elemental Analysis for $C_{13}H_{20}O_3$ calcd: C, 69.61; H, 8.99, found: C, 69.54; H, 9.12.

3.1.5. 2-(1-Phenyl-propanoyloxyméthyl)cyclopent-2-en-1-one (2e)

IR ($CHCl_3$) cm^{-1}: 1743 (C=O, ester), 1701 (C=O, ketone). ^1H NMR (300 MHz, $CDCl_3$): 7.48 (m, 1H), 7.37-7.18 (m, 5H), 6.54 (s, 1H), 2.58 (m, 2H), 2.45-2.29 (m, 4H), 1.17 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 206.5, 171.9, 159.2, 145.4, 138.2, 128.4, 128.3, 127.2, 70.2, 34.9, 27.6, 26.6, 9.0. MS (m/z): 57(98), 77(28), 109(55), 128 (97), 141(16), 141(16), 159(14), 171(20), 187(100), 244 (M^+; 2). Elemental Analysis for $C_{15}H_{16}O_3$ calcd: C, 73.75; H, 6.60, found: C, 73.78; H, 6.71.

CONCLUSION

In the present study, we have reported the preparation of the (±) HomoSarkomycine Ester **2a** in one step from 2-hydroxymethl-2-cyclopentenone **1a**. We have succeeded to generalize this process with Baylis-Hillman adducts **1b-e**. Local reactivity descriptors are shown to be very powerful in predicting the reactivity of Baylis-Hillman adducts **1a-e**, propanoic acid and triethylorthoester.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at Qassim University for funding this research group No (3208).

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

REFERENCES

[1] Marx, J.N.; Minaskanian, G. 2-Carbemethoxycyclopentenone as a Synthon. Synthesis of sarkomycin. *Tetrahedron Lett*., **1979**, *43*, 4175-4178.

[2] Marx, J.N.; Minaskanian, G. Regiospecific synthesis of sarkomycin and some analogs. *J. Org. Chem.,* **1982**, *47*, 3306-3310.

[3] Rui, T.; Ken-Ichiro, W.; Noboru, O.; Yukio, Y. Asymmetric synthesis of 3-substitueted 2-exo-methylenealkanones by addition-elimination reaction using a chiral leaving and organometallic nucleophiles. *J. Org. Chem*., **1992**, *57*, 4895-4903.

[4] Barreiro, E.J. A new synthesis of Sarkomycin. *Tetrahedron Lett*., **1982**, *23*, 3605-3607.

[5] Misumi, A.; Furuta, K.; Yamamoto, H. A new and unusually flexible route to cyclopentenoids synthesis of sarkomycin and prostaglandins. *Tetrahedron Lett.,* **1984**, *25*, 671-674.

[6] Otera, J.; Niibo, Y.; Aikawa, H. The efficient consecutive b-carboxylation and a-alkylation of cyclic a,b-enones : A new route to sarkomycin. *Tetrahedron Lett*., **1987**, *28*, 2147-2150.

[7] Mikolajczyk, M.; Zurawinski, R.; Kielbasinski, P. A new synthesis of (±)-sarkomycin from a b-ketophosphonate. *Tetrahedron Lett*., **1989**, *30*, 1143-1146.

[8] Jankowski, K. Synthese de l'Homosarkomycin racemique. *Tetrahedron Lett*., **1971**, *20*, 1733-1735.

[9] Vidal, J.; Huet, F. Synthesis of a-methlenecyclobutanones. First preparation of norsakomycin methylester. *J. Org. Chem*., **1988**, *53*, 611-616.

[10] Amri, H.; Rambaud, M.; Villieras, J. A short large scale synthesis of (±)-sarkomycin esters. *Tetrahedron Lett*., **1989**, *30*, 7381-7382.

[11] Beji, F.; Besbes, R.; Amri, H. Synthesis of a-alkylidene-b-ethoxycarbonyl cyclopentanones and g-butyrolactones. *Synth. Commun*., **2000**, *30*, 3947-3954.

[12] Samarat, A.; Landais, Y.; Amri, H. First synthesis of (±)-bis-homosarkomycin ethyl ester. *Tetrahedron Lett.,* **2004**, *45*, 2049-2050.

[13] Hoffmann, H.M.R.; Rabe, J. Synthesis and biological activity of a-methylene-g-butyrolactones. *Angew. Chem., Int. Ed. Engl.,* **1985**, *24*, 94-110.

[14] Park, B.K.; Nakagawa, M.; Hirota, A.; Nakayama, M. Methylenolactocin, anovel antitumor antibiotic from penicilium SP. *J. Antibiot.,* **1988**, *6*, 751.

[15] Christian, C.; George H.B.; Hans W. Synthesis of cis-hedione and methyl jasmonate *via* cascade Baylis-Hillman reaction and claisen ortho ester rearrangement. *Helvetica Chimica Acta,* **2005**, *88*, 3069-3088.

[16] Wexler, B.A.; Toder, B.H.; Minaskanian, G.; SmithIII, A.B. Efficient regiocontrolled synthesis of sarkomycin and homosarkomycin. *J. Org. Chem.,* **1982**, *47*, 3333-3335.

[17] Tanimori, S.; Kainuki, T.; Nakamaya, M. Synthesis of (±)-homosarkomycin and (±)-Rosaprostol. *Biosci. Biothec. Biochem.*, **2014**, *56*, 1807-1809.

[18] Lee, E.; Hur, C.-U.K.; Park, J.-H. Intramolecular cyclisation of acetylenic homoallylic ketones mediated by the addition of stannyl radicals: A short facile pathway to a-metylene-b-substituted cyclopentanones. *Tetrahedron Lett*., **1989**, *30*, 7219-7220.

[19] Erin, J.; Julie, L.E.; Diana, S.H.; Haibo, W.; Heekyung, T.; Zhebo, D.; Bruce, G.; Donald, J.C. Molecular basis of the antitumor activities of 2-crotonyloxymethyl-2-cycloalkenones *J. Med. Chem*., **2003**, *46*, 194-196.

[20] Ian, F.; Pranab, M.; Chandrashekar, R. Stereocontrol of 1,5-related stereocentres using an intermediate silyl group-the diastereoselectivity of nucleophilic attack on a double bond adjacent to a stereogenic centre caring a silyl group *Org. Biomol. Chem.,* **2003**, *1*, 3989-4004.

[21] Gatri, R.; Rezgui, F.; El Gaied, M.M. Nouvelle voie d'accès aux cyclopenténones b'-fonctionnelles b-substituées : synthèse d'une substance odorante. *J. de la Société Chimique de Tunisie*, **2006**, *8*, 167-173.

[22] Rezgui, F.; El Gaied, M.M. Réaction régiospécifique des carbanions stabilisés avec la 2-(acétoxyméthyl)cyccohex-2-én-1-one : synthèse de diénones cycliques. *Tetrahedron*, **1997**, *53*, 15711.

[23] Rezgui, F.; El Gaied, M.M. An efficient one pot synthesis of bicyclic Dienones. *J. Chem. Res. (S)*, **1999**, *8*, 510-511.

[24] Gatri, R.; El Gaied, M.M. Imidazole-catalyzed Baylis-Hillman reactions : a new route to allylic alcohols from aldehydes and cyclic enones. *Tetrahedron Lett*., **2002**, *43*, 7835-7836.

[25] Fernandes, R.A.; Chowdhury, A.K.; Kattanguru, P. The orthoester Johnson-Claisen rearrangement in the synthesis of bioactive molecules, natural products and synthetic intermediates – recent advances *Eur*. *J. Org. Chem.*, **2014**, *14*, 2833-2871.

[26] Zhao, Y.; Truhlar, D.G. Density functionals for noncovalent interaction energies of biological importance. *J. Chem. Theory Comput*., **2007**, *3*, 289-300.

[27] Zee, C.; W.; Parr, R.G. Development of the colle-salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B*, **1988**, *37*, 785.

[28] Gaussian 09, Revision A.1, M.J. Frisch and all. Gaussian, Inc., Wallingford CT, **2009**.

[29] Arfaoui, Y.; Efrit, M.L.; Besbes, N. Theoretical investigations on the mechanistic pathway of the thermal rearrangement of substituteted N-acyl-2,2-dimethylaziridines. *J. Mol. Model*., **2013**, *19*, 4603-4612.

[30] Geerlings, P.; De Proft, F.; Langenaeker, W. Conceptual density functional theory. *Chem. Rev.,* **2003**, *103*, 1793-1873.

[31] Fitzgerald, G. On the use of fractional charges for computing Fukui Functions. *Mol. Simul.*, **2008**, *34*, 931-936.