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Pd-catalyzed domino reactions of nitroaromatics: A surrogate access towards the saturated *N*-heterocycles

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ABSTRACT

Using Pd/HCOOCs as a surrogate reagents synthesis of saturated *N*-heterocycles was described from nitroaromatics as starting materials. The developed new reaction conditions exclude the generally used toxic reagents like carbon monoxide as deoxygenative agent. The developed protocol permits the synthesis privileged bioactive *N*-heterocyclic scaffolds in good yields and selectivity.

In recent years synthesis of heterocycles gained considerable impact in the field of medicinal chemistry due to their occurrence in a broad range of biologically active compounds and in marketed drug molecules.[1–3] Among the heterocyclic scaffolds, the preparation of saturated *N*-heterocycles have emerged considerable attention due to their solitary chemical, biological and pharmacological properties.[4,5] Their unique chemical and pharmacological profile inspired chemist towards novel syntheses of saturated *N*-heterocycles.[4,5] Abundance of these key structural motifs in naturally occurring bioactive compounds as well as in pharmaceuticals alleges a sound impact to admit them into an important class of compounds (Fig. 1).[4,5] Hence, during the recent years the development of mild and atom economy methods for the synthesis of *N*-heterocycles with distinct substitution motifs has emerged as a field of augmenting points of pursuit in organic synthesis.[1–5] Among the devoted efforts towards the synthesis of saturated *N*-heterocycles a broad range of traditional protocols involving the formation of C-N bonds have been dedicated. The most useful, straightforward and widely explored approaches for the preparation of saturated *N*-heterocycles refers to the reductive cyclization of nitroaromatics, nucleophilic substitution and dipolar cycloaddition reaction.[4–6] Miserably, myriad of these methods often agonizes from limitations such as the use of a large excess of deoxygenative agents and drastic reaction conditions.[4–6] Interestingly, a collection of surrogate methods based on the palladium-catalyzed C—N bond formation have also been evolved in the past years to serve this purpose.[4a,6j] Among the saturated *N*-heterocycles 1,4-benzothiazines, 1,4-benzoxazines and tetrahydroquinolines scaffolds received considerable attention to chemist.[6h–j] In this regards, last few years literature witnessed an enormous amounts of work for their synthesis using ω-nitroalkenes as easy available starting materials and the key step of the reactions hinged upon reductive cyclization of nitroaromatics.[6h–j] However, most importantly the previously presented methods rely on the use of excess P(III) reagents and molecular carbon monoxide as deoxygenative agents leading to the formation of the corresponding oxides in the first case. Both excess P(III) reagents as well as its corresponding oxides remains difficult to remove from the reaction mixtures. On the other hand, the use of highly toxic carbon monoxide molecule as deoxygenative agent hampers the application of this method. Nevertheless, the early report towards the synthesis of 1,4-bezoxazines and tetrahydroquinolines associated with the use of excess triethyl phosphite as deoxygenative agent that suffers from the unavoidable limitation due to the formation of considerable amounts of corresponding *N*-ethylated side products.[6h,i] The limitation of the parent report associated with the formation of side product was repaired using

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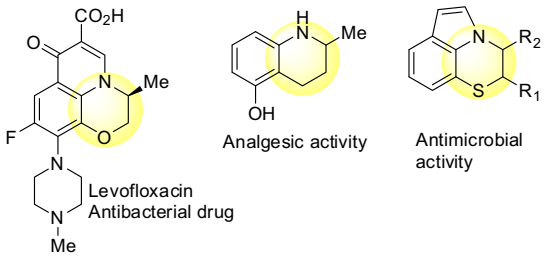
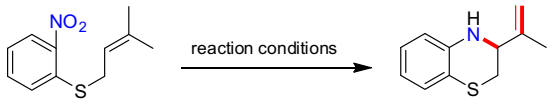


Figure 1. Selected examples of saturated *N*-heterocycles.

reaction of ω-nitroalkenes in presence of Mo(VI) as catalyst and triphenylphosphine as deoxygenative agent.[7] Unfortunately, the use of P(III) reagents still remains a major drawbacks of the existing reported protocols towards the synthesis of these structural motifs. Therefore, the development of a novel method that excludes the use of P(III) reagents to achieve the synthesis of saturated *N*-heterocycles is highly desired. Having extensively reviewed the reported works associated with the preparation of saturated *N*-heterocycles starting from nitroaromatics, we focused on exploring this transformation using ω-nitroalkenes as substrate since these classes of compounds are very seldom studied under Pd-catalyzed transformation.[6j] Additionally, the current work targeted on developing surrogate transformation of ω-nitroalkenes to saturated *N*-heterocycles avoiding the use of P(III) reagents. Hence, in order to achieve this purpose ω-nitroalkenes were used as model substrates and a mixture of Pd-catalyst in presence of Lewis acid, and cesium formate (HCOOCs) as reducing agent were explored as reaction conditions. A careful literature study revealed that there is still no report on the reductive cyclization of nitroaromatics using a mixture of Pd-catalyst and cesium formate as reagents. In context, a plethora of other reagents have been investigated towards the reductive cyclization of nitroaromatics.[1–6] Here we disclose a mild and efficient synthetic protocol for the preparation of 1,4-benzothiazines, 1,4-benzoxazines and tetrahydroquinolines using ω-nitroalkenes as cheap starting material based on easy to operate domino reaction.

To begin with the preliminary screening of reaction conditions the starting ω-nitroalkenes were prepared using the previously reported methods.[6h,i,7] The starting material 2-nitrophenyl thioether **1a** was considered as a model substrate and interestingly, a reaction of **1a** in presence of 0.05 equiv. of $PdCl_2$ as catalyst and 3 equivs. of HCOOCs as reducing agent in DMF as solvent at 120 °C for 16 h in sealed vial afforded the desired 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzo-thiazines **2a** (Table 1, entry 1). In order to investigate the detailed and efficient reaction conditions for the effective conversion of **1a** to **2a**, next the reactions were carried out in the presence of 0.05 equiv. of $PdCl_2$ as catalyst, 0.15 equiv. of an additive and 3 equivs. of HCOOCs as reducing agent in DMF as solvent at 120 °C for 16 h in sealed vial (Table 1, entries 2–11). Among the additives applied during the optimization studies (Table 1, entries 2–11), it was observed that $SnCl_2$ revealed the highest efficacy towards the transformation of **1a** to **2a** with the isolated yield of 31% (Table 1, entry 8). Moreover, additives such as $MoCl_5$, $FeCl_3$, TfOH and AcOH were proved to be not suitable for this transformation leading to the formation of complex mixture of compounds (Table 1, entries 4 and 9–11). It was also observed that the use of surrogate reducing agent delivered unsatisfactory results

Table 1
Preliminary screening of the reaction conditions for the transformation of **1a** to **2a**.[a]

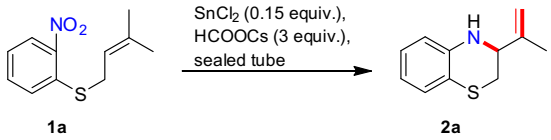


1a **2a**

Entry	Conditions	**2a**, Yield%
1	$PdCl_2$ (0.05 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	9[b]
2	$PdCl_2$ (0.05 equiv.), $ZnCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	15[b]
3	$PdCl_2$ (0.05 equiv.), $TiCl_4$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	6[b]
4	$PdCl_2$ (0.05 equiv.), $MoCl_5$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
5	$PdCl_2$ (0.05 equiv.), $CuCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	19[b]
6	$PdCl_2$ (0.05 equiv.), $In(OTf)_3$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	17[b]
7	$PdCl_2$ (0.05 equiv.), $Yb(OTf)_3$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	14[b]
8	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	31[b]
9	$PdCl_2$ (0.05 equiv.), $FeCl_3$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
10	$PdCl_2$ (0.05 equiv.), TfOH (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
11	$PdCl_2$ (0.05 equiv.), AcOH (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
12	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), $HCOONH_4$ (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
13	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOONa (3 equiv.), DMF, 120 °C, 16 h, sealed tube	5[b]
14	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOK (3 equiv.), DMF, 120 °C, 16 h, sealed tube	9 [b]
15	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOH (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
16	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.10 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	26 [b]
17	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.05 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	15 [b]
18	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOCs (2 equiv.), DMF, 120 °C, 16 h, sealed tube	19 [b]
19	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOCs (1 equiv.), DMF, 120 °C, 16 h, sealed tube	8 [b]
20	$SnCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	-[d,b]
21	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), DMF, 120 °C, 16 h, sealed tube	- [d,b]

[a] Unless otherwise indicated, all reactions were performed using **1a** (1 mmol) in dry DMF (2 mL) under mentioned conditions.
[b] Starting material recovered.
[c] Complex mixture observed on TLC which was not purified.
[d] Cleavage of the starting material was observed.

Table 2
Screening of the Pd-catalysts for the transformation of ω-nitroalkene **1a** to saturated *N*-heterocycle **2a**.[a]



1a **2a**

Entry	Pd-catalyst (equiv.)	Solvent	T (°C)/t (h)	**2a**, Yield%
1	$Pd(OAc)_2$ (0.05)	DMF	120/16	27 [b]
2	$Pd(OTf)_2$ (0.05)	DMF	120/16	39 [b]
3	$Pd_2(dba)_3$ (0.05)	DMF	120/16	16 [b]
4	$Pd(PPh_3)_4$	DMF	120/16	51 [b]
5	**$PdCl_2(PPh_3)_2$ (0.05)**	**DMF**	**120/16**	**81**
6	$PdCl_2(dppf) \cdot CH_2Cl_2$ (0.05)	DMF	120/16	78
7	$PdCl_2(PPh_3)_2$ (0.05)	DMSO	120/16	39 [b]
8	$PdCl_2(PPh_3)_2$ (0.05)	DMF/DMSO [c]	120/16	65
9	$PdCl_2(PPh_3)_2$ (0.05)	1,4-Dioxane	120/16	33[b]
10	$PdCl_2(PPh_3)_2$ (0.05)	MeCN	120/16	19[b]
11	$PdCl_2(PPh_3)_2$ (0.05)	PhMe	120/16	21[b]
12	$PdCl_2(PPh_3)_2$ (0.05)	AcOH	120/16	Complex mixture[d]
13	$PdCl_2(PPh_3)_2$ (0.05)	1,4-Dioxane/H_2O [e]	120/16	Complex mixture[d]
14	$PdCl_2(PPh_3)_2$ (0.05)	IsoPropanol	120/16	Complex mixture[d]
15	$PdCl_2(PPh_3)_2$ (0.05)	DMF	140/16	77
16	$PdCl_2(PPh_3)_2$ (0.05)	DMF	80/16	43[b]
17	$PdCl_2(PPh_3)_2$ (0.05)	DMF	100/16	61[b]
18	$PdCl_2(PPh_3)_2$ (0.05)	DMF	120/10	53[b]
19	$PdCl_2(PPh_3)_2$ (0.05)	DMF	120/24	79
20	$PdCl_2(PPh_3)_2$ (0.10)	DMF	120/16	80
21	$PdCl_2(PPh_3)_2$ (0.03)	DMF	120/16	59
22	$PdCl_2(PPh_3)_2$ (0.01)	DMF	120/16	36 [b]

It shows the conditions giving highest yield of the final product.
[a] Unless otherwise indicated, all reactions were performed using **1a** (1 mmol) in dry solvent (2 mL) under mentioned conditions.
[b] Starting material recovered.
[c] 2 mL DMF/DMSO in 10:1 ratio was used as solvent.
[d] Complex mixture observed on TLC which was not purified.
[e] 2 mL 1,4-dioxane/H_2O in 4:1 ratio was used as solvent.

(Table 1, entries 12–15). Interestingly, the yield of the desired product was consistently decreasing when the reactions were carried out with decreasing amounts of both additive and reducing agent (Table 1, entries 16–19). However, it is important to note that in absence of Pd-catalyst as well as reducing agent the cleavage of starting material was observed (Table 1, entries 20–21).

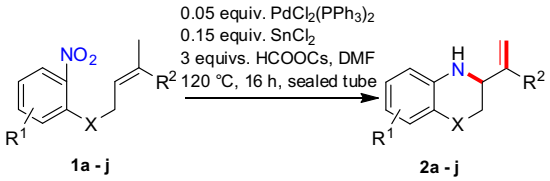
In order to investigate the efficient conditions for the conversion of **1a** to **2a**, the reaction conditions were further optimized using a broad range of Pd-catalysts (Table 2, entries 1–6). Among the Pd-source attempted to serve this purpose, the $PdCl_2(PPh_3)_2$ as catalyst delivered the highest yield of **2a** (Table 2, entry 5). Moreover, after careful optimizations of the reaction conditions with regard to the reaction parameters such as solvent, reaction temperature, and time as well as the amounts of Pd-catalyst (Table 2, entries 7–22), it was concluded that when 1 mmol of **1a** was reacted in presence of 0.05 equiv. of $PdCl_2(PPh_3)_2$ as catalyst, 0.15 equiv. of $SnCl_2$ as an additive and 3 equivs. of HCOOCs as reducing agent in DMF as solvent at 120 °C for 16 h in sealed vial leading to the formation of the desired product **2a** with highest yield (Table 2, entry 5). Therefore, these reaction conditions were considered as optimal conditions for the synthesis of related saturated *N*-heterocycles (Table 3).

Finally, the scope of the developed method has been extended for the preparation of related heterocycles by exploring the substrate of choice under the optimal conditions. It was investigated that afar from the synthesis of 3,4-dihydro-2*H*-1,4-benzothiazines **2a**-**c**, the developed methods can also be successfully applied towards the preparation of 3,4-dihydro-2*H*-1,4-benzoxazines **2d**-**i**, and 1,2,3,4-tetrahydroquinoline **2j** (Table 3). Interestingly, substrates **1a**-**j** was well tolerated under the optimized reaction conditions to afford the corresponding saturated *N*-heterocycles **2a**-**j** in high yields (Table 3).

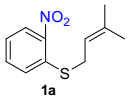
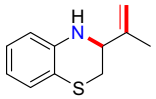
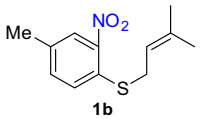
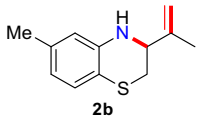
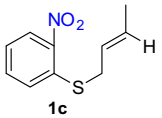
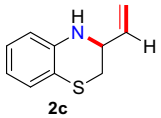
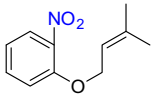
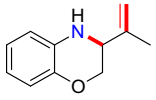
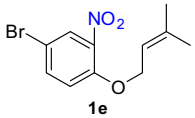
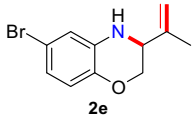
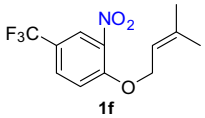
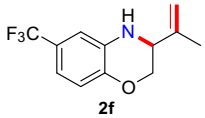
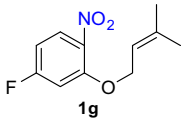
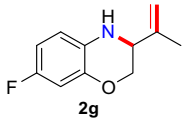
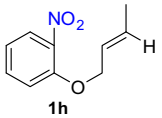
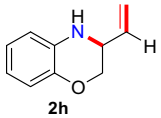
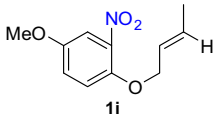
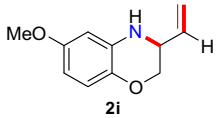
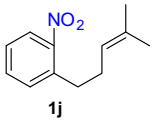
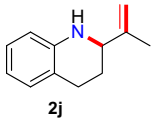
A proposal for the plausible reaction mechanism for the conversion of **1a** into **2a** is drawn in Scheme 1. Successive deoxygenation of nitroaromatics **1a** leading to the formation of the intermediate **C**. It is assumed that the decomposition of HCOOCs delivers *in situ* generated CO molecules which may be responsible for the deoxygenation process in the presence of catalytic amounts of palladium. However, the formation of expected four-membered palladacycles could facilitate in the presence of $SnCl_2$ which may coordinate to the oxygen atom of nitro group due to its Lewis acid character. In next step, a four membered palladacycle **D** can be formed via [2+2] cycloaddition of the intermediate **C**. The intermediate **D** followed by cleavage due to hydride transfer results in the formation of intermediate **E** which via reductive elimination may afford the corresponding cyclized product **2a**.

To summarize, we have investigated a new, efficient and mild surrogate protocol for the synthesis of saturated *N*-heterocycles using simple nitroaromatics as starting materials. The newly developed method avoids the use of highly toxic and hazardous reagents like P(III)-reagent and molecular carbon monoxide. During the present work cesium formate was used as an additive which served the purpose of carbon monoxide molecule to perform the cyclization reaction with such rarely explored ω-nitroalkenes. Under the reaction conditions the starting materials were well tolerated to deliver the corresponding saturated *N*-heterocycles in good to excellent yields. The investigated reaction conditions may find enormous application in the field of reductive cyclization of nitroaromatics.

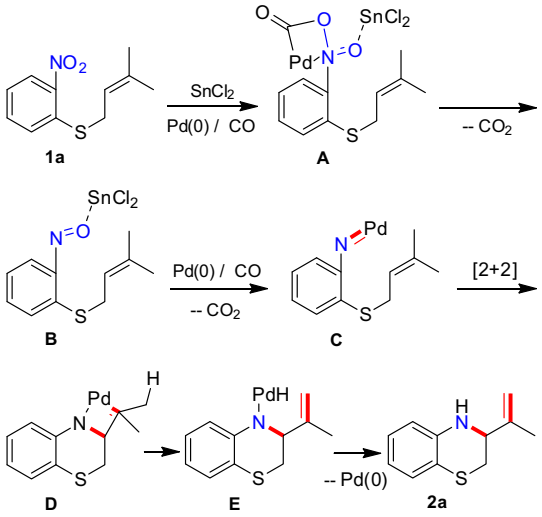
Table 3
Pd-Catalyzed synthesis of saturated *N*-heterocycles.[a]



X = S, R^1 = H, R^2 = CH_3,	**1a**	X = O, R^1 = CF_3, R^2 = CH_3,	**1f**
X = S, R^1 = CH_3, R^2 = CH_3,	**1b**	X = O, R^1 = F, R^2 = CH_3,	**1g**
X = S, R^1 = H, R^2 = H,	**1c**	X = O, R^1 = H, R^2 = H,	**1h**
X = O, R^1 = H, R^2 = CH_3,	**1d**	X = O, R^1 = OMe, R^2 = H,	**1i**
X = O, R^1 = Br, R^2 = CH_3,	**1e**	X = CH_2, R^1 = H, R^2 = CH_3,	**1j**

Entry	Substrate	Product	Yield% [b]
1	 **1a**	 **2a**	81
2	 **1b**	 **2b**	79
3	 **1c**	 **2c**	73
4	 **1d**	 **2d**	85
5	 **1e**	 **2e**	71
6	 **1f**	 **2f**	59
7	 **1g**	 **2g**	66
8	 **1h**	 **2h**	77
9	 **1i**	 **2i**	63
10	 **1j**	 **2j**	69

[a] Unless otherwise indicated, all reactions were performed using **1a-j** (1 mmol) in dry DMF (2 mL) under optimal conditions.
[b] Isolated yields of the product.



Scheme 1. Proposed reaction mechanism for the conversion of **1a** to **2a**.

Experimental section

General experimental procedure for the Pd-catalyzed Synthesis of saturated N-Heterocycles

A 10 mL pressure tube was charged with a mixture of **1a** (1.0 mmol, 223 mg), $PdCl_2(PPh_3)_2$ (0.05 mmol, 35 mg), anhydrous $SnCl_2$ (0.15 mmol, 28.5 mg), HCOOCs (3.0 mmol, 534 mg) and dry DMF (2 mL). The pressure tube was then sealed and heated at 120 °C for 16 h. After completion of the reaction, the mixture was diluted with hot ethyl acetate (30 mL) and water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (3 × 20 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography over silica gel using hexane/ethyl acetate = 20:1 as an eluent to obtain the desired product **2a** in 81% (155 mg) yield as light yellow oil.

*Synthesis and characterization of 3-Isopropenyl-3,4-dihydro-2H-benzo[1,4] thiazine (**2a**)*[7]

Light yellow oil; R_f = 0. 56 (SiO_2, hexane/EtOAc = 20:1); **^{1}H NMR** (300 MHz, $CDCl_3$, δ ppm): δ = 1.85 (s, 3H, 3′-H), 2.96 (overlapped, 1H, 3-H), 2.97 (dd, ^3J = 3.9 Hz, ^2J = 12.5 Hz, 1H, 2b-H), 3.05 (dd, ^3J = 7.3 Hz, ^2J = 12.5 Hz, 1H, 2a-H), 4.06 (brdd, ^3J = 3.9 Hz, ^3J = 7.2 Hz, 1H, 3-H), 5.05 (brs, 1H, 2′-H), 5.14 (brs, 1H, 2′-H), 6.52 (dd, ^3J = 8.0 Hz, ^2J = 1.3 Hz, 1H, 5-H), 6.65 (ddd, ^3J = 7.5 Hz, ^3J = 7.5 Hz, ^2J = 1.3 Hz, 1H, 7-H), 6.91 (ddt, ^3J = 7.3 Hz, ^3J = 8.0 Hz, ^2J = 1.6 Hz, 1H, 6-H), 7.03 (dd, ^3J = 7.8 Hz, ^2J = 1.5 Hz, 1H, 8-H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.24 (C-3′), 30.17 (C-2), 57.18 (C-3), 112.93 (C-2′), 115.63 (C-5), 115.89 (C-9), 118.53 (C-7), 125.95 (C-6), 127.72 (C-8), 142.06 (C-10), 145.79 ppm (C-1′); **MS** (EI, 70 eV): *m*/*z* (%) = 191.1 (100) (M^+), 163.1 (18), 150.1 (46), 117.1 (21), 109.0 (11), 65 (5).

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.11.037.

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