Accepted Manuscript

Merging metathesis and photochemical Csp^3-H activation: Access to masked β-formyl hexanolides and their rearrangement to furofuranones

Quentin Glenadel, Youssef Nassar, Ludovic Raffier, Sebastiaan Veys, Olivier Piva

PII: S0040-4020(18)30740-3

DOI: 10.1016/j.tet.2018.06.040

Reference: TET 29636

To appear in: *Tetrahedron*

Received Date: 1 March 2018

Revised Date: 14 June 2018

Accepted Date: 15 June 2018

Please cite this article as: Glenadel Q, Nassar Y, Raffier L, Veys S, Piva O, Merging metathesis and photochemical Csp^3-H activation: Access to masked β-formyl hexanolides and their rearrangement to furofuranones, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.06.040.

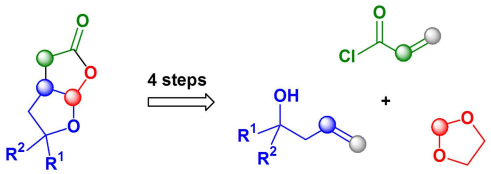
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Merging metathesis and photochemical Csp^3-H activation: Access to β-formyl hexanolides and their rearrangement to furofuranones

Leave this area blank for abstract info.

Quentin Glenadel, Youssef Nassar, Ludovic Raffier, Sebastiaan Veys and Olivier Piva*
Université de Lyon – ICBMS – UMR 5246 CNRS –France



Tetrahedron
journal homepage: www.elsevier.com

Merging metathesis and photochemical Csp^3-H activation: Access to masked β-formyl hexanolides and their rearrangement to furofuranones

Quentin Glenadel[a] , Youssef Nassar[a] , Ludovic Raffier[a] , Sebastiaan Veys[a] , and Olivier Piva[a,] ∗
[a]*Université de Lyon, Université Claude Bernard Lyon 1,CNRS, CPE Lyon, INSA-Lyon, UMR 5246, ICBMS, Bat. Raulin, 43, Bd du 11 novembre 1918, F-69622 Villeubanne cedex, France*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ring-closing metathesis
Lactones
Radical addition
Photochemistry
Deprotection

ABSTRACT

β-Masked formyl hexanolides were prepared by a three-step sequence including esterification of homoallylic alcohols, ring-closing metathesis and the photochemically induced addition of dioxanyl radical. When treated under oxidative conditions, the adducts underwent cleavage of the ketal group leading after rearrangement to parent furofuranones, structures found in some biological active compounds.

∗ Corresponding author. Tel.: +33-047-244-8136; e-mail: piva@university-lyon1.fr

1. Introduction

Unsaturated five and six membered-ring lactones constitute two important classes of compounds largely present in the nature.[1] They are also considered as promising scaffolds for the access to more elaborated targets. Since the discovery and availability of well-defined catalysts, ring-closing metathesis has emerged as a powerful method to access a large number of unsaturated heterocyclic structures, including these lactones.[2-4] Furthermore, the newly created double bond can be subsequently functionalized to deliver more sophisticated compounds.[5] In connection with our interest in metathesis but also in photochemical reactions, we have merged these two topics to develop a synthesis of masked formyl hexanolides, which could be further transformed into furofuranones. Such bicyclic subunits have been found in numerous natural products, which exhibit for a large part of them, interesting properties. For exemple, 15-oxoscutecyprol A **1**, a neoclerodane derivative is an effective antifeedant compound with potential interest for biological control against pests.[6] Norrisolide **2** has a major impact on the Golgi apparatus in eukaryotic cells, and induces its irreversible fragmentation.[7] Compound **3** which possesses a 5,6-*seco* tremulane skeleton[8] as well as conosilane A **4**,[9] have been recently isolated from cultures of basidiomycete *Conocybe siliginea*. Therefore, due to their biological properties, access to furofuranones and related structures has been the subject of intense investigations over the past thirty years.[10-17]

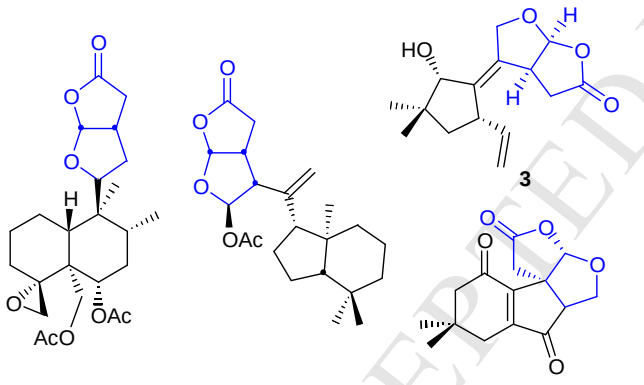
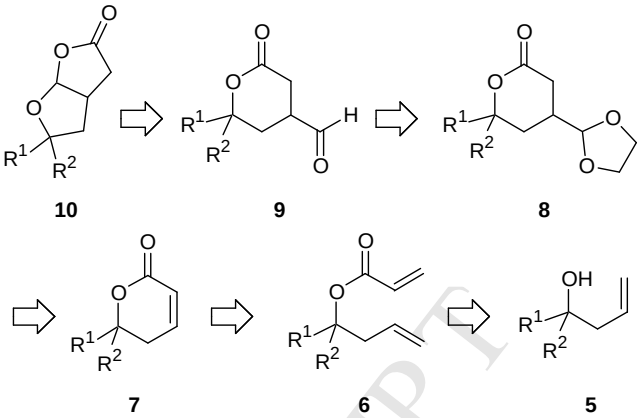


Figure 1. Natural products possessing a furofuranone subunit.

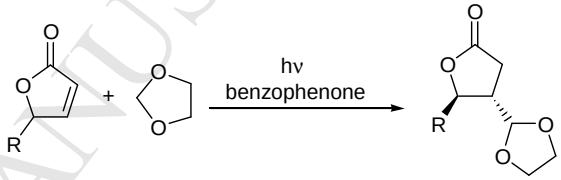
2. Results and discussion

We envisaged the access to furofuranones as illustrated in scheme 1. Readily available homoallylic acrylates **6** could deliver the corresponding α,β–unsaturated δ-valerolactones **7** by ring-closing metathesis (RCM). It was anticipated that the addition of a highly stabilized dioxolanyl radical generated by hydrogen abstraction from the solvent, could regioselectively occur to furnish the expected masked β-formyl adducts **8**. A selective deprotection of the ketal group, followed by a rearrangement of the formyl lactones could deliver the corresponding furofuranones **10**.



Scheme 1. Planned synthetic pathway to furofuranones **10**.

The conversion of **7** into **8** is based on previous results[18] already conducted on butenolides and other electron deficient alkenes. Photochemical hydrogen abstraction on 1,3-dioxolane promoted by benzophenone could generate a highly stabilized radical which underwent a regio- and diastereoselective addition onto the conjugated double bond. (Scheme 2).



Scheme 2. Photochemical addition of 1,3-dioxolane on butenolides.

The benefits of this process are manifold. First, the conditions are mild avoiding the use of strong bases on highly sensitive substrates. Furthermore, the process can be conducted in the presence of only catalytic amounts of benzophenone as a promoter.[19] Gratifying, the reaction was carried out under visible light, avoiding the use of special equipments. In the intensive field of C-H activation and functionalization of organic substrates at a specific position, the photochemical approach appears also extremely attractive in term of cost, compared to other transformations which usually require the use of noble metals such as palladium or ruthenium even in catalytic amounts.

Known secondary homoallylic alcohols **5a-b** were efficiently prepared by condensation of allylzinc on aldehydes under Barbier conditions.[20] Esterification[21] with acryloyl chloride furnished homoallylic acrylates **6a-b**. RCM was then carried out by reflux of dichloromethane and in presence of 5 mol% of Grubbs type I catalyst **GB$_I$** (Fig. 2). After 4 to 6 hours of heating, the unsaturated lactones **7a-b** were obtained with high yields (Table 1).

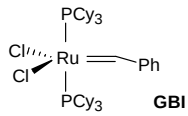
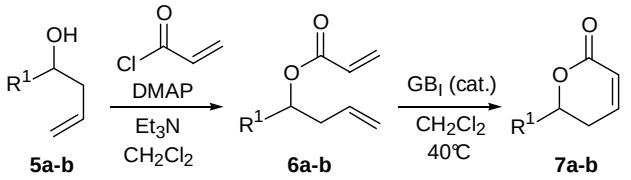


Figure 2. Grubbs type I catalyst.

Table 1. Synthesis and RCM of acrylates **6a-b**.



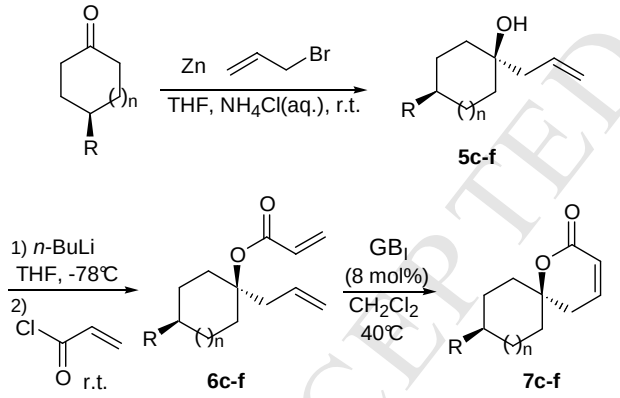
5a-b **6a-b** **7a-b**

5	R_1	6	Yield[a]	7	Yield[a]
5a	*n*-C_8H_{17}	**6a**	61%	**7a**	76%
5b	*m*-CH_3O-C_6H_4	**6b**	75%	**7b**	83%

[a] Isolated yield

In parallel, formation of spiranic lactones[22] was carried out from cyclic tertiary homoallylic alcohols **5c-f**, easily prepared by treatment of cycloalkanones with *in situ* generated allyl zinc reagent. Esterification of these hindered alcohols was achieved by deprotonation with *n*-BuLi, followed by reaction with acryloyl chloride.[21b] By this way, esters **6c-f** were isolated in acceptable yields. Successful RCM required at least a suitable conformation by the substrate for which the two double bonds are close. We were highly pleased to notice that even in the presence of less reactive Grubbs type I catalyst **GB_I**, the reaction occurred rapidly to furnished the spiranic lactones, without the need of additives as titanium isopropoxide. This efficiency could be attributed to a Thorpe Ingold effect which allows a favourable conformation to the substrates.[23]

Table 2. Synthesis and RCM of acrylates **6c-f**.



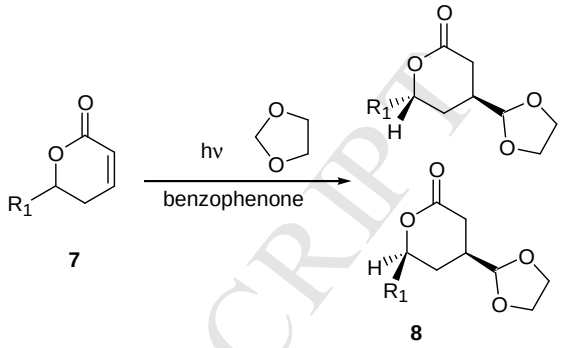
5c-f **6c-f** **7c-f**

5	R	n	Yield%[a]	6	Yield%[a]	7	Yield%[a]
5c	H	0	Quant.	**6c**	47	**7c**	75
5d	H	1	90	**6d**	57	**7d**	87
5e	*t*-Bu	1	68	**6e**	72	**7e**	77
5f	Ph	1	76	**6f**	46	**7f**	76

[a] Isolated yield

Radical addition was first carried out on lactones **7a-b**. The reaction requires usually 4 to 6 hours of irradiation in 1,3-dioxolane as solvent and under argon to prevent competitive oxidations. The attack of the stabilized radical occurred exclusively on the β-position to furnish a new radical intermediate which abstracted one hydrogen atom. After chromatography, compounds **8a-b** were tentatively purified by flash-chromatography to furnish a mixture of *syn/anti* stereoisomers but still contaminated with some minor dioxolane derivatives (Table 3).

Table 3. Addition of dioxalanyl radical onto lactones **7a-b**

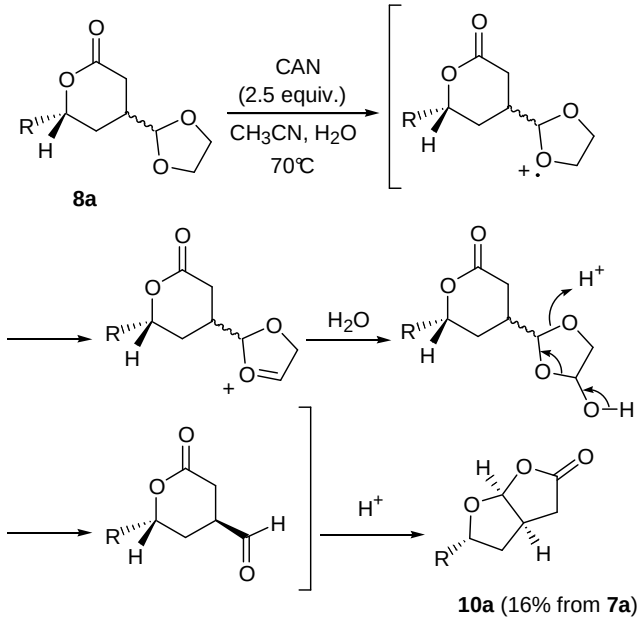


7 **8**

7	R_1	8	*syn:anti*[a]
7a	*n*-C_8H_{17}	**8a**	34:66
7b	*m*-CH_3O-C_6H_4	**8b**	25:75

[a] Determined by ^{1}H-NMR on the isolated product.

To have an access to the free formyl derivatives, various conditions were tested to deprotect the ketal group. Initial attempts have been carried out on compound **8a** under acidic conditions leading to the recovery of starting material or decomposition when performed at rt or higher temperatures respectively. Reactions involving oxidative deprotection were next considered.[24] According to the literature, cerium ammonium nitrate (CAN) can promote single electron transfer to generate a radical cation which can be oxidized in the middle and undergo the subsequent deprotection.

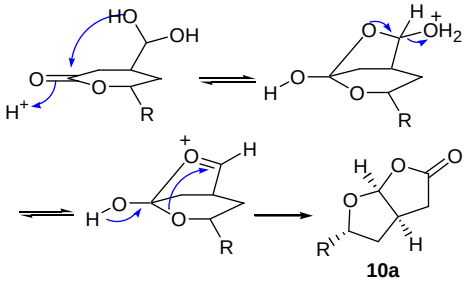


8a **10a** (16% from **7a**)

Scheme 3. Oxidative deprotection of **8a** and direct access to **10a**.

As expected, β-formyl lactone **8a**, when treated by CAN in a 2:1 mixture of acetonitrile and water, was converted to a new

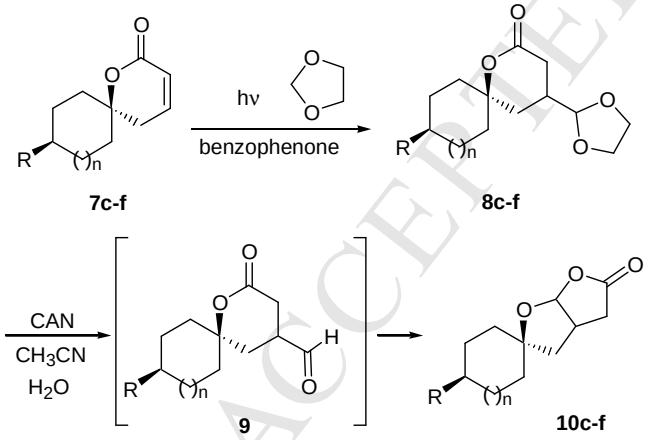
structure. ^{1}H-NMR spectra analysis was not consistent with the presence of a free aldehyde function, but revealed nevertheless the cleavage of the dioxanolyl subunit. On ^{13}C-NMR spectra, signal at 108 ppm was characteristic of the new ketal group of furofuranones (Scheme 3). Based on these observations and previous results in the literature,[12,14,25] it was assumed that the formation of the furofuranone occurred during the deprotection step and can be rationalized by the following mechanism (Scheme 4). This procedure was also applied to **8b** but unfortunately, decomposition of the starting material was solely observed. In this case, a competitive oxidation could take place on the additional benzylic position leading to degradation.



Scheme 4. Rearrangement of formyllactone into furofuranone **10**.

Spirohexenolides **7c-f** were submitted to the photochemical assisted radical addition of dioxolane furnishing β-masked formyl lactones **8c-f** which were also contaminated by minor side-products of similar polarity. After removal of the solvent, the crude product was submitted to CAN oxidation to furnish furifuranones **10c-f** (Table 4).

Table 4. Addition of dioxalanyl radical onto spiranic lactones **7c-f**

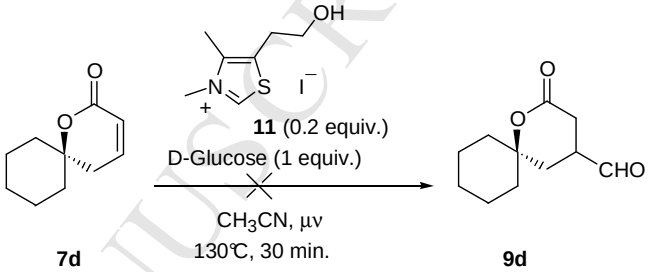


7	R	n	10	Yield[a]
7c	H	0	**10c**	48%
7d	H	1	**10d**	46%
7e	*t*-Bu	1	**10e**	48%
7f	Ph	1	**10f**	40%

[a] Isolated yield

Compounds **10c-f** were obtained in the range of 40 to 48% yield. It should be pointed out that these values result from three-step processes which include in each case, a regioselective addition of the dioxanyl radical, a deprotection of the ketal group and finally the rearrangement of formyl lactones to furofuranones.

Additionally, to explore an alternative pathway to β-formyl hexanolides **9** from lactones **7**, we investigated a Stetter type reaction[26] by using the conditions reported by Chi *et al.* on chalcones.[27] D-Glucose combined with commercially available thiazolium salt **11** was used to generate a formyl anion in CH_3CN under microwaves activation (Scheme 5). Unfortunately, when performed on **7d**, the starting material was integrally recovered even after prolonged microwave irradiation.



Scheme 5. Alternative approach to β-formylhexanolide.

3. Conclusions

In conclusion, we have reported the synthesis of protected β-formyl hexanolides by merging a RCM and an intermolecular regioselective dioxanyl radical addition. This overall process which combines an organometallic catalyzed cyclization and a photochemical reaction can be considered as an attractive *green* process. It demonstrates once again the interest to develop photochemical procedures and reinforce its role in the field of sustainable chemistry. Consequently, deprotection of the ketal group was achieved under oxidative conditions leading after rearrangement to furofuranones in moderate yields.

4. Experimental section

4.1 General

All commercially available compounds were used without further purification. Solvent were dried according to standard procedures. Hexanes refer to a hydrocarbon mixture with a boiling range of 40-60°C. Column chromatography was performed with silica gel (0.040-0.063 mm, ROTH). NMR spectra were recorded at 293 K, using a 300 MHz spectrometer (Bruker, AMX 300). Shifts are referenced relative to deuterated solvent residual peaks. Low and high resolutions (BR and HRMS) mass spectra were recorded in the positive mode using a Bruker MicrOTOF-Q II XL spectrometer. IR spectra were recorded on a Perkin Elmer Spectrum One apparatus. Irradiation were performed in pyrex vessel with a 500W white halogen lamp (Massive Faro model with a maximum of emission between 300 and 800 nm).

4.2. Allylation of cycloalkanones – General procedure.[28]

To a stirred solution of the cycloalkanone (12.9 mmol) in a 1:1 THF and saturated ammonium chloride solution (0.2M), were

added allyl bromide (19.3 mmol) and zinc (1.27 g, 19.3 mmol). The whole mixture was stirred for 16 h at room temperature. After complete disappearance of the starting material (TLC control), THF was removed by concentration. After dilution with ether, the aqueous layer was extracted with ether (2x 10 mL). The organic phase was further dried with $MgSO_4$. After filtration and concentration, the crude product was purified by flash-chromatography over silica with a 90:10 hexanes : EtOAc solution as eluent to give the expected compounds. Spectroscopic data were in agreement with literature: **5c**[29](78 %), **5d**[30] (93%), **5e**[31] (67%), **5f**[32] (71%).

4.3 Esterification of secondary homoallylic alcohols – General procedure.[21a]

To a solution of homoallylic alcohol **5a-b** (2 mmol) in DCM (10 mL) was added triethylamine (2.2 mmol) and DMAP (0.1 mmol). After cooling to 0°C, acryloyl chloride (4 mmol) was dropwise added. The resulting mixture was stirred at r.t. for 4h. After hydrolysis with a saturated aqueous solution of ammonium chloride, the aqueous layer was extracted with DCM. The organic layers were successively washed with water and brine, then dried over $MgSO_4$. After filtration and concentration, the resulting solution was purified by flash chromatography on silica (10/90 EtOAc/hexanes).

4.4. 4-Dodec-1-enyl acrylate (**6a**)

Colorless oil. Yield: 61% (318 mg isolated from **5a** (401 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.39 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.83-5.69 (m, 2H), 5.11-5.03 (m, 3H), 2.37-2.31 (m, 2H), 1.59-1.57 (m, 2H), 1.28-1.21 (m, 12H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 166.1, 133.9, 130.5, 129.0, 117.8, 73.8, 38.8, 33.7, 32.0, 29.6, 29.4, 25.4, 22.8, 14.3. HRMS (ESI): m/z [M+Na^+] calcd for $C_{15}H_{26}NaO_2$: 261.1825; found: 261.1820.

4.5. 1-(3-Methoxyphenyl)but-3-enyl acrylate (**6b**)[33]

Colorless oil. Yield: 71% (1.70 g isolated from **5b** (1.85 g)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.29-7.24 (m, 1H), 6.95-6.88 (m, 2H), 6.83 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H), 6.43 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.15 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.87-5.81 (m, 2H), 5.72 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.12-5.03 (m, 2H), 3.81 (s, 3H), 2.74-2.54 (m, 2H). ^{13}C RMN (75 MHz, $CDCl_3$): δ (ppm) = 165.4, 159.7, 141.7, 133.3, 131.0, 129.6, 128.6, 118.9, 118.2, 113.3, 112.4, 75.3, 55.3, 40.9. HRMS (ESI): m/z [M+Na^+] calcd for $C_{14}H_{16}NaO_3$: 255.0992; found: 255.0980.

4.6. Esterification of tertiary alcohols – General procedure.[21b]

A solution of the homoallylic alcohol (2.89 mmol) in dry THF (40 mL) was treated with a 1.6 M solution of *n*-BuLi in hexane (2.1 mL, 3.47 mmol) at –78 °C for 1 h. Acryloyl chloride (0.35 ml, 4.33 mmol) was then added, and the mixture was warmed to r.t. and stirred overnight. After hydrolysis with a saturated $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 12 mL). After drying over anhydrous $MgSO_4$, the organic layers were concentrated under reduced pressure and the crude product was purified by column chromatography using 90:10 Petroleum ether: EtOAc as eluent to give the corresponding acrylate**.**

4.7. 1-Allylcyclopentyl acrylate (**6c**)

Colorless oil. Yield: 47% (343 mg isolated from **5c** (511 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.30 (dd, *J* = 17.3, 1.7 Hz, 1H), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.84-5.70 (m, 2H), 5.10-5.01 (m, 2H), 2.76 (dt, *J* = 7.3, 1.2 Hz, 2H), 2.17-2.08 (m, 2H), 1.81-1.53 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.7, 133.9, 130.1, 129.7, 118.0, 92.2, 41.5, 37.4, 24.1. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{11}H_{16}NaO_2$: 203.1043; found: 203.1038.

4.8. 1-Allylcyclohexyl acrylate (**6d**)

Yellow oil. Yield: 57% (180 mg isolated from **5d** (290 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.32 (dd, *J* = 17.3, 1.7 Hz, 1H), 6.07 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.82-5.68 (m, 2H), 5.09-5.02 (m, 2H), 2.69 (dt, *J* = 7.3, 1.1 Hz, 2H), 2.25 (d, *J* = 12.2 Hz, 2H), 1.62-1.21 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.4, 133.1, 130.3, 129.6, 118.3, 83.8, 42.2, 34.6, 25.6, 21.9. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{12}H_{18}NaO_2$: 217.1199; found: 217.1193.

4.9. 1-Allyl-4-t-butylcyclohexyl acrylate (**6e**)

Colorless oil. Yield: 72% (260 mg isolated from **5e** (284 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.28 (dd, *J* = 17.3, 1.7 Hz, 1H), 6.02 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.75-5.66 (m, 2H), 5.04-4.98 (m, 2H), 2.64 (d, *J* = 7.5 Hz, 2H), 2.41-2.37 (m, 2H), 1.58-1.55 (m, 2H), 1.24-1.16 (m, 4H), 1.01-0.93 (m, 1H), 0.80 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.2, 133.0, 130.2, 129.4, 118.2, 83.0, 47.3, 42.8, 34.7, 32.4, 27.5, 22.3. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{16}H_{26}NaO_2$: 273.1825; found: 273.1821.

4.10. 1-Allyl-4-phenylcyclohexyl acrylate (**6f**)

Colorless oil. Yield: 37% (504 mg isolated from **5f** (1070 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32-7.16 (m, 5H), 6.38 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.13 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.86-5.70 (m, 2H), 5.13-5.06 (m, 2H), 2.75 (d, *J* = 7.4 Hz, 2H), 2.57-2.49 (m, 1H), 1.79-1.63 (m, 4H), 1.57-1.21 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 165.0, 146.7, 132.7, 130.0, 129.6, 128.3, 126.7, 126.0, 118.4, 82.4, 43.3, 42.7, 34.5, 29.0. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{18}H_{22}NaO_2$: 293.1512; found: 293.1512.

4.11. Metathesis:

A solution of acrylate **6** (1.85 mmol) in dichloromethane (185 mL) was deoxygenated by bubbling an argon stream through the solution for 10 min. Grubbs type I catalyst (120 mg, 0.15 mmol) was added in one portion, and the resulting homogeneous solution was heated for 2-4 h. After concentration, lactone **7** was isolated by flash-chromatography on silica (EtOAc/hexanes, 20:80).

4.12. 6-Octyl hexenolide (**7a**)

Brown oil. Yield: 76% (195 mg isolated from **6a** (290 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.90-6.84 (m, 1H), 6.02 (dt, *J* = 9.7, 1.7 Hz, 1H), 4.46-4.37 (m, 1H), 2.35-2.31 (m, 2H), 1.68-1.60 (m, 2H), 1.34-1.21 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 164.8, 145.2, 121.6, 78.2, 35.0, 32.0, 29.6, 29.6,

29.5, 29.4, 25.0, 22.8, 14.3. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{13}H_{22}NaO_2$: 233.1512; found: 233.1509.

4.13. 6-(3-Methoxyphenyl) hexenolide (**7b**)[34]

Brown oil. Yield: 89% (384 mg isolated from **6b** (490 mg)). ^{1}H RMN (300 MHz, $CDCl_3$): δ (ppm) = 7.29 (t, *J* = 8.2 Hz, 1H), 6.99-6.93 (m, 3H), 6.88 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1H), 6.12 (dt, *J* = 9.8, 1.9 Hz, 1H), 5.42 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.81 (s, 3H), 2.65-2.60 (m, 2H). ^{13}C RMN (75 MHz, $CDCl_3$): δ (ppm) = 164.0, 159.7, 145.2, 140.0, 129.7, 121.4, 118.2, 114.0, 111.5, 79.0, 55.3, 31.6. HRMS (ESI): m/z [M+Na+] calcd for $C_{12}H_{12}NaO_3$: 227.0679; found: 227.0670.

4.14. 6-Oxaspiro[4,5]decen-8-en-7-one (**7c**)[35]

Brown oil. Yield: 75% (181 mg isolated from **6c** (284 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.84 (dt, *J* = 9.8, 4.3 Hz, 1H), 6.02 (dt, *J* = 9.8, 1.9 Hz, 1H), 2,52 (dd, *J* = 4.3, 1.9 Hz, 2H), 2.12-2.04 (m, 2H), 1.93-1.86 (m, 2H), 1.70-1.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 164.6, 144.6, 121.6, 90.8, 38.9, 34.0, 23.7. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_9H_{12}NaO_2$: 175.0730; found: 175.0725.

4.15. 1-Oxaspiro[5,5]undecen-3-en-2-one (**7d**)

Brown oil. Yield: 87% (135 mg isolated from **6d** (180 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.63 (dt, *J* = 9.8, 4.3 Hz, 1H), 6.01 (dt, *J* = 9.8, 2.0 Hz, 1H), 2.40 (dd, *J* = 9.8, 2.0 Hz, 2H), 2.01-1.94 (m, 2H), 1.81-1.70 (m, 2H), 1.58-1.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 164.0, 143.2, 121.2, 81.4, 36.5, 34.7, 25.5, 21.7. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{10}H_{14}NaO_2$: 189.0886; found: 189.0879.

4.16. 1-Oxaspiro-9-t-butyl[5,5]undecen-3-en-2-one (**7e**)

White solid. M_p = 101-102°C. Yield: 81% (130 mg isolated from **6e** (180 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.70 (dt, *J* = 9.8, 4.3 Hz, 1H), 5.93 (dt, *J* = 9.8, 2.2 Hz, 1H), 2,30 (dd, *J* = 4.4, 2.2 Hz, 2H), 2.17-2.10 (m, 2H), 1.57-1.38 (m, 4H), 1.33-1.20 (m, 2H), 1.02-0.88 (m, 1H), 0.81 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 163.8, 143.4, 120.9, 80.2, 47.7, 36.8, 36.0, 32.4, 27.6, 21.8. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{14}H_{22}NaO_2$: 245.1512; found: 245.1516.

4.17. 1-Oxaspiro-9-phenyl[5,5]undecen-3-en-2-one (**7f**)

White solid. M_p = 113-114°C. Yield: 76% (340 mg isolated from **2f** (500 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.32-7.17 (m, 5H), 6.77 (dt, *J* = 9.2, 4.2 Hz, 1H), 6.02 (dt, *J* = 9.2, 1.9 Hz, 1H), 2.54 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.40 (dd, *J* = 4.2, 1.9 Hz, 2H), 2.31-2.23 (m, 2H), 2.02 (qd, *J* = 13.6, 3.9 Hz, 2H), 1.76-1.70 (m, 2H), 1.52 (td, *J* = 13.6, 3.9 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 163.6, 146.3, 143.4, 128.3, 126.8, 126.1, 120.8, 79.7, 43.6, 36.4, 35.8, 28.3.HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{16}H_{18}NaO_2^+$: 265.1199; found: 265.1205.

4.18. Access to furofuranones – General procedure

4.18.1 Irradiation of lactone **7**

A solution of unsaturated lactone **7** (0.9 mmol) dissolved in 1,3-dioxolane (100 mL) was placed in a 250 mL pyrex balloon equipped with a cooling system. Benzophenone (25 mg, 0.14 mmol.) was added and the resulting clear solution was bubbled with argon for 10 min. Irradiation was carried out until complete disappearance of the starting material (TLC control). The solution was concentrated under vacuum. Compounds **8a** and **8b** were tentatively purified by flash-chromatography on silica (eluant 20:80 AcOEt:hexanes). Other lactones **8c-8f** obtained as crude mixture, were directly implicated in the next deprotection / rearrangement procedure without further purification.

4.18.2 Deprotection of the dioxolane / rearrangement

To the crude mixture obtained after irradiation (1 mmol) dissolved in a 1:2 solution of acetonitrile and water was added in one portion at 60°C, cerium ammonium nitrate (1.36g, 2.5 mmol). The resulting mixture was heated at 70°C until complete disappearance of the starting material. After cooling to r.t., the aqueous phase was extracted with diethylether (3 x 10mL). The combined organic layers were dried over $MgSO_4$. After filtration and concentration, the resulting mixture was purified by flash-chromatography over silica (eluent: 35/65 AcOEt/hexanes).

4.19. Furofuranone (**10a**)

Colorless oil. Yield: 16% (23 mg isolated from **7a** (122 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 5.95 (d, *J* = 4.9 Hz, 1H), 4.22 (p, *J* = 7.0 Hz, 1H), 3.12-3.01 (m, 1H), 2.80 (dd, *J* = 17.9, 8.5 Hz, 1H), 2.53-2.38 (m, 2H), 1.75-1.64 (m, 1H), 1.57-1.21 (m, 14H), 0.87 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.4, 108.8, 83.5, 40.1, 37.0, 36.8, 36.2, 32.0, 29.6, 29.6, 29.4, 26.2, 22.8, 14.2. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{14}H_{24}NaO_3$: 263.1618; found: 263.1618. IR (ATR): 1776 (C=O), 1111 (C-O) cm^{-1}.

4.20. Furofuranone (**10c**)

Colorless oil. Yield: 48% (100 mg isolated from **8c** (177 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.03 (d, *J* = 5.5 Hz, 1H), 3.18 (dddd, *J* = 9.9, 5.5, 4.6, 2.8 Hz, 1H), 2.84 (dd, *J* = 18.4, 9.9 Hz, 1H), 2.49 (dd, *J* = 18.4, 2.8 Hz, 1H), 2.27 (dd, *J* = 13.1, 9.5 Hz, 1H), 2.01-1.57 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 175.2, 108.9, 95.3, 42.0, 39.6, 39.4, 39.3, 36.2, 24.4, 23.5. IR ($CHCl_3$): ν (cm^{-1}) = 2958, 2871, 1769, 1451, 1177, 1112, 962. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{10}H_{14}NaO_3$: 205.0835; found: 205.0838. IR (ATR): 1770 (C=O), 1113 (C-O) cm^{-1}.

4.21. Furofuranone (**10d**)

Colorless oil. Yield: 46% (57 mg isolated from **8d** (153 mg)). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.00 (d, *J* = 5.3 Hz, 1H), 3.20-3.08 (m, 1H), 2.81 (dd, *J* = 18.1, 8.9 Hz, 1H), 2.47 (dd, *J* = 18.1, 1.7 Hz, 1H), 2.18 (dd, *J* = 13.1, 9.9 Hz, 1H), 1.74-1.32 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.9, 109.0, 88.6, 42.1, 39.5, 39.0, 38.2, 36.8, 25.2, 23.6, 23.6. IR ($CHCl_3$): ν (cm^{-1}) = 2931,

2856, 1762, 1418, 1129, 1122, 909. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{11}H_{16}NaO_3$: 219.0992; found: 219.0986. IR (ATR): 1762 (C=O), 1123 (C-O) cm^{-1}.

4.22. Furofuranone (**10e**)

White solid. M_p = 139-140°C. Yield: 48% (41 mg isolated from **8e** (101 mg)). ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 6.02 (d, *J* = 5.3 Hz, 1H), 3.20-3.09 (m, 1H), 2.81 (dd, *J* = 18.2, 9.0 Hz, 1H), 2.48 (dd, *J* = 18.2, 1.9 Hz, 1H), 2.11 (dd, *J* = 13.1, 9.9 Hz, 1H), 1.83 (dt, *J* = 9.1, 2.7 Hz, 1H), 1.74 (dt, *J* = 9.8, 2.9 Hz, 1H), 1.64-1.51 (m, 3H), 1.47-1.34 (m, 4H), 1.01-0.92 (m, 1H), 0.85 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.9, 109.2, 87.1, 47.3, 43.8, 39.2, 38.9, 38.7, 36.7, 32.5, 27.6, 23.6, 23.4. IR ($CHCl_3$) : ν (cm^{-1}) = 2938, 2861, 1774, 1446, 1150, 1104, 928. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{15}H_{24}NaO_3$: 275.1618; found: 275.1611. IR (ATR): 1774 (C=O), 1105 (C-O) cm^{-1}.

4.23. Furofuranone **(10f)**

White solid. M_p = 151-152°C. Yield: 40% (112 mg isolated from **8f** (251 mg)).^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.31-7.15 (m, 5H), 6.05 (d, *J* = 5.3 Hz, 1H), 3.23-3.12 (m, 1H), 2.82 (dd, *J* = 18.1, 9.0 Hz, 1H), 2.53-2.44 (m, 2H), 2.19 (dd, *J* = 13.3, 9.7 Hz, 1H), 2.03-1.68 (m, 6H), 1.65-1.50 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 174.7, 146.9, 128.5, 127.0, 126.2, 109.1, 86.7, 43.9, 43.4, 39.3, 38.7, 38.5, 36.7, 30.2, 30.2. IR ($CHCl_3$): ν (cm^{-1}) = 2935, 2875, 1757, 1413, 1196 1115, 950. HRMS (ESI): *m/z* [M+Na^+] calcd for $C_{17}H_{20}NaO_3$: 295.1305; found: 295.1310. IR (ATR): 1757 (C=O), 1114 (C-O) cm^{-1}.

Acknowledgement

L.R. and Y.N. both thank the Ministère de la Recherche et de l'Enseignement Supérieur for a Ph-D grant. S.V. thanks the E.U. Erasmus program exchange. Financial supports from Université de Lyon, Institut de Chimie de Lyon (ICL) and CNRS are also warmly acknowledged.

References and notes

(1) (a) Marco JA, Carda M, Murga J, Falomir E. *Tetrahedron* 2007; 63:2929-2958; (b) Bassetti M, D'Annibale A. *Curr. Org. Chem.* 2013; 17:2654-2677; (c) Spulak M, Ghavre M, Pour M. *Tetrahedron Lett.* 2017; 58:263-270.

(2) van Lierop BJ, Lummiss JAM, Fogg DE. In *Olefin metathesis*, Grela, K. Ed.; Wiley-VCH: Hoboken, N.J., 2014, pp. 85-152.

(3) (a) Prunet J. *Eur. J. Org. Chem.* 2011; 3634-3647; (b) Kotha S, Dipak MK. *Tetrahedron* 2012; 68:397-421 ; (c) Schmid TE, Dumas A, Colombel-Rouen S, Crévisy C, Baslé O, Mauduit M. *Synlett* 2017; 28:773-798.

(4) Nolan SP, Clavier H. *Chem. Soc. Rev.* 2010; 39:3305-3316.

(5) Alcaide B, Almendros P, Luna A. *Chem. Rev.* 2009; 109:3817-3858.

(6) Rosselli S, Maggio A, Piozzi F, Simmonds MSJ, Bruno M. *J. Agric. Food Chem.* 2004; 52:7867-7871.

(7) Guizzinti G, Brady TP, Fischer D, Malhotra V, Theodorakis EA. *Bioorg. Med. Chem.* 2010; 18:2115-2122.

(8) Yang X-Y, Feng T, Ding J-H, Yin X, Guo H, Li Z-H, Liu J-K. *Nat. Prod. Bioprospect.* 2013; 3:48-51.

(9) Yang X-Y, Feng T, Li Z-H, Yin X, Leng Y, Liu J-K. *Org. Lett.* 2012; 14:5382-5384.

(10) (a) Schmidt B, Hoffmann HMR. *Tetrahedron* 1991; 47:9357-9368; (b) Trost BM, Toste, FD. *J. Am. Chem. Soc.* 2003; 125:3090-3100.

(11) (a) Petit F, Furstoss R. *Tetrahedron: Asymmetry* 1993; 4:1341-1352; (b) Gebbinck, EA, Bouwman CT, Bourgois M, Jansen BJM, de Groot A. *Tetrahedron* 1999; 55:11051-11076 ; (c) Donate PM, da Silva R, da Silva GVJ, Aleman C. *Synth. Commun.* 2001; 31:141-150 ; (d) Malanga C, Mannucci S, Lardicci L. *J. Chem. Research (S)*, 2001; 97-99; (e) Alonso F, Rodriguez-Fernandez M, Sanchez D, Yus M. *Synthesis* 2010; 3013-3020; (f) Schnermann M J, Beaudry CM, Genung NE, Canham SM, Untiedt NL, Karanikolas BDW, Sütterlin C, Overman LE. *J. Am. Chem. Soc.* 2011; 133:17494-17503; (g) Sridhar PR, Reddy GM, Seshadri K. *Eur. J. Org. Chem.* 2012; 6228-6235; (h) Garnsey MR, Slutskyy Y, Jamison CR, Zhao P, Lee J, Rhee YH, Overman LE. *J. Org. Chem.* DOI: 10.1021/acs.joc.7b02458 ; (i) Zhao WW, Liu Y-K. *Org. Chem. Front.* 2007; 4:2358-2363.

(12) (a) Bujons J, Sanchez-Baeza F, Messeguer A. *Tetrahedron* 1994; 50:7597-7610; (b) Uenishi J'I, Muraoka H, Namaki M, Hata N. *Synthesis* 2004; 1343-1348.

(13) (a) Toyota M, Hirota M, Nishikawa Y, Fukumoto K, Ihara M. *J. Org. Chem.* 1998; 63:5895-5902; (b) Fehring V, Knights S, Chan M-Y, O'Neil IA, Cosstick R. *Org. Biomol. Chem.* 2003; 1:123-128; (c) Marino JP, Kieler KA, Kim M-W. *Tetrahedron* 2011; 67:837-841.

(14) Enders D, Vazquez J, Raabe G. *Eur. J. Org. Chem.* 2000, 893-901.

(15) Uchiyama M, Hirai M, Nagata M, Katoh R, Ogawa R, Ohta A. *Tetrahedron Lett.* 2001; 42:4653-4656.

(16) (a) Kim C, Brady T, Kim SH, Theodorakis, EA. *Synth. Commun.* 2004; 34:1951-1955; (b) Brady TP, Kim SH, Wen K, Kim C, Theodorakis EA. *Chem. Eur. J.* 2005; 11:7175-7190; (c) Weisser R, Yue W, Reiser O. *Org. Lett.* 2005; 7:5353-5356; (d) Harrar K, Reiser O. *Chem. Commun.* 2012; 48:3457-3459.

(17) Granger K, Casaubon RL, Snapper ML. *Eur. J. Org. Chem.* 2012; 2308-2311.

(18) (a) Ghosh A, Leshchenko S, Noetzel M. *J. Org. Chem.* 2004; 69:7822-7829; (b) Fraser-Reid B, Anderson RC, Hicks DH, Walker DL. *Can. J. Chem.* 1977; 55:3986-3995; (c) Paquette LA, Pansegrau PD, Wiedeman PE, Springer JP. *J. Org. Chem.* 1988; 53:1461-1466; (d) Graalfs H, Fröhlich R, Wolff C, Mattay J. *Eur. J. Org. Chem.* 1999; 1057-1073; (e) Campari G, Fagnoni M, Mella M, Albini A. *Tetrahedron: Asymmetry* 2000; 11: 1891-

1906; (f) Dondi D, Protti S, Albini A, Carpio SM, Fagnoni M. *Green Chem.* 2009; 11:1653-1659.

(19) (a) Lerch S, Unkel L-N, Wienefeld P, Brasholz M. *Synlett* 2014; 25:2673-2680; (b) Hoffmann N. *J. Phys. Org. Chem.* 2015; 28:121-136.

(20) Jogi A, Mäeorg U. *Molecules* 2001; 6:964-968.

(21) (a) Cros F, Pelotier B, Piva O. *Eur. J. Org. Chem*. 2010; 5063-5070; (b) Gerbino DC, Mandolesi SD, Koll LC, Podesta JC. *Synthesis* 2005; 2491-2496.

(22) Kotha S, Deb AC, Lahiri K, Manivannan E. *Synthesis* 2009; 165-193.

(23) (a) Kim YJ, Grimm JB, Lee D. *Tetrahedron Lett.* 2007; 45:7961-7964; (b) Hoye TR, Jeon J, Tennakoon MA. *Angew. Chem. Int. Ed*. 2011; 50:2141-2143.

(24) (a) Ates A, Gautier A, Leroy B, Plancher J-M, Quesnel Y, Vanherck J-C, Marko IE. *Tetrahedron* 2003; 59:8989-8999; (b) Maulide N, Marko IE. *Synlett* 2005; 2195-2198.

(25) Moufid N, Chapleur Y, Mayon P. *J. Chem. Perkin Trans 1*, 1992; 991-998.

(26) (a) Grossmann A, Enders D. *Angew. Chem. Int. Ed*. 2012; 51:314-325; (b) Flanigan DM, Romanov-Michailidis F, White NA, Rovis T. *Chem. Rev.* 2015; 115:9307-9387.

(27) Zhang J, Xing C, Tiwari B, Chi YR *J. Am. Chem. Soc.* 2013; 135:8113-8116.

(28) Pratihar S, Kakoty A, Sarmah K. *New J. Chem.* 2016; 40:5347-5356.

(29) Brady WT, Giang Y-SF, Weng L, Dad MM. *J. Org. Chem.* 1986; 52:2216-2220.

(30) Guijarro D, Mancheño B, Yus M. *Tetrahedron* 1992; 48: 4593-4600.

(31) Kataoka Y, Makihira I, Yamagata T, Tani K. *Organometallics* 1997; 16:4788-4795.

(32) Schneider U, Kobayashi S. *Angew. Chem. Int. Ed.* 2007; 46:5909-5912.

(33) Deng Y, Pan W, Pei Y-N, Li J-L, Bai B, Zhu H-J. *Tetrahedron* 2013, 69:10431-10437.

(34) Lee S-M, Lee W-G, Kim Y-C, Ko H. *Bioorg. & Med. Chem. Lett.* 2011; 21:5726-5729.

(35) Yeom H-S, Koo J, Park H-S, Wang Y, Liang Y, Yu Z-X, Shin S. *J. Am. Chem. Soc.* 2012; 134:208-211.