RSC Advances




ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

ARTICLE

# Total synthesis and stereochemical assignment of cryptolatifolione†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Luiz F. T. Novaes,[a] Ariel M. Sarotti[b] and Ronaldo A. Pilli[a,]*

An enantioselective total synthesis of cryptolatifolione and its C-8 epimer is presented in a protecting-group-free fashion. The synthesis relied on the use of a catalytic double Krische allylation, catalytic olefin metathesis and a C-H oxidation. Comparison of spectroscopic data of the synthetic isomers and natural product made possible the unequivocally elucidation of the absolute configuration of cryptolatifolione.

## Introduction

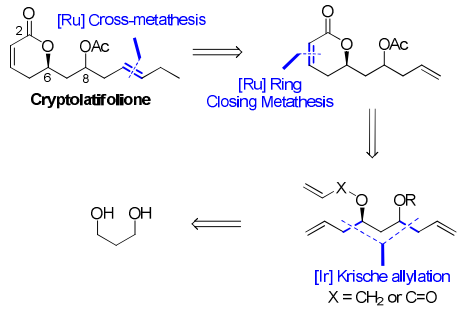
Dihydropyranone motif is found in several natural products from different sources. Fostriecin (CI-920),[1] bitungolide A[2] and cryptomoscatone D2[3] contain this motif and were isolated from bacteria *Streptomyces pulveraceus*, from the sponge *Theonella swinhoei*, and from the bark of the tree *Cryptocaria mandiocanna*, respectively.

Compounds containing dihydropyranone ring display a broad range of pharmacological properties, including antitumoral,[4] antimicrobial[5] and antiparasite[6] activity, inhibition of HIV protease[7] and hepatitis C virus polymerase,[8] induction of apoptosis[9] and molluscicidal properties.[10]

This class have attracted considerable interest from synthetic research groups, from 2006 to 2012, over 60 targets being accomplished by total synthesis.[11] We have reported the total synthesis and structural elucidation of some dihydropyranones in recent years, such as coibacins A-B,[12] and cryptomoscatones D1 and D2.[13]

In this context, we drove our attention to a natural lactone isolated by Wijewardene and coworkers from the bark of *Cryptocaria latifolia* in 1996, christened by us as cryptolatifolione.[14] The configuration of the stereogenic center at C-6 was assigned by the authors as *R*, but the configuration at C-8 remains unknown (see Scheme 1). In this communication, we report a total synthesis of cryptolatifolione and its C-8 epimer, envisioning structural elucidation.

Assuming the absolute stereochemistry at C-6 as *R*, we planned the synthesis of two epimers at C-8 in order to establish unequivocally the absolute configuration of cryptolatifolione with C-C bonds being constructed by catalytic methods: a double Krische allylation of commercially available 1,3-propanediol (**1**) employing iridium catalysis, followed by ring closing metathesis (RCM) and an *E*-selective cross metathesis, to secure the six-membered ring and the *E*-double bond, respectively (Scheme 1).



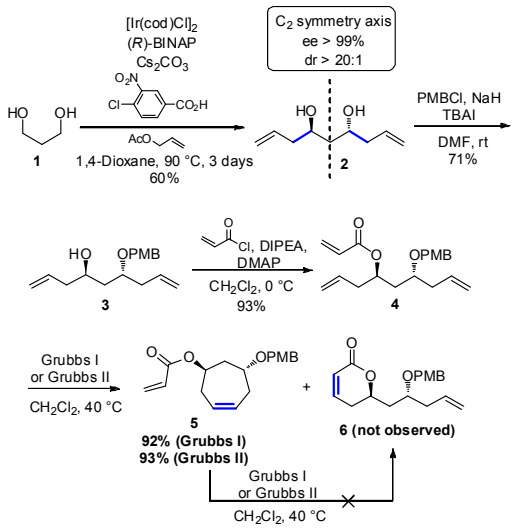

Scheme 1. Retrosynthetic plan for cryptolatifolione

## Results and discussion

Synthesis of acrylate **4** began with the enantioselective iridium catalyzed allylation of commercial 1,3-propanediol (**1**)[15] to provide diol **2** in 60% yield, diastereoisomeric ratio higher than 20:1 and enantiomeric excess higher than 99% (Scheme 2).[16] The $C_2$-symmetric diol **2** was monoprotected as the PMB ether in 71% yield, followed by esterification with acryloyl chloride to afford acrylate **4** in 93% yield. In the next step, we aimed to construct the dihydropyran-2-one moiety via the ring closing metathesis reaction of acrylate **4**, but we were surprised to observe the exclusive formation of the seven-membered ring **5** using Grubbs' catalyst I (92% yield) or II (93% yield). In order to circumvent this undesired reactivity, we exposed cycloheptene **5** to Grubbs' catalyst I or II, in refluxing $CH_2Cl_2$ for few days, aiming to promote a sequence of ring opening/ring closing metathesis which might lead to the desired dihydropyran-2-one **6**.[17] Unfortunately, only cycloheptene **5** was recovered after these attempts (Scheme 2).

[a] *Departamento de Química Orgânica, Instituto de Química, Universidade Estadual de Campinas (Unicamp), CP 6154, CEP 13084-971, Campinas, São Paulo, Brazil.*
[b] *Instituto de Química Rosario, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario-CONICET, Suipacha 531, S2002LRK Rosario, Argentina.*

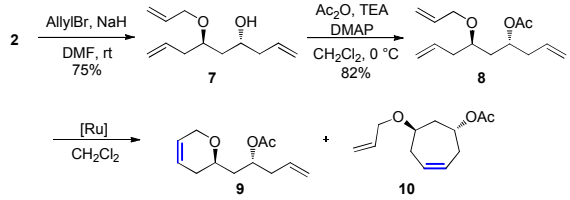
† Electronic Supplementary Information (ESI) available: copies of $^1$H and $^{13}$C NMR spectra of products, HPLC, GC chromatograms and computational methods. See DOI: 10.1039/x0xx00000x




Scheme 2. First approach to cryptolatifolione

Triene **4** is composed by two olefins of type I (allylic) and one olefin of type II (acrylate), using the classification when by Grubbs and coworkers.[18] Considering that reaction between two olefins of type I is faster than a reaction of one olefin of type I and another of type II,[18] and the inertness of cycloheptene **5** to ring opening/ring closing metathesis (Scheme 2), we decided to replace the acrylate (type II) by an allyl group (type I), and install the carbonyl in a later stage *via* a C-H oxidation. Furthermore, in this approach, the PMB group would be replaced by an acetate, which is part of the structure of cryptolatifolione, thus envisioning a protecting group-free synthesis.

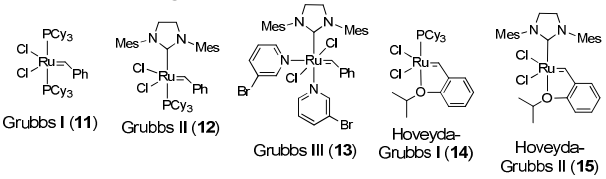
In order to explore such approach, $C_2$-symmetric diol **2** was treated with allyl bromide to produce alcohol **7** in 75% yield, followed by esterification with acetic anhydride in 71% yield (Scheme 3). In the ring-closing metathesis reaction step, we tested five commercial ruthenium catalysts (**11**-**15**, Table 1). Catalyst **11** and **14** furnished low selectivity in favor of dihydropyran **9** (entries 1 and 4). Although we observed a discrete increment in the selectivity upon reduction of reaction temperature with catalyst **11**, it was accompanied with a decrease in the yield (entry 2). Eventually, catalysts containing *N*-heterocyclic carbene (NHC) ligand showed high yields and high selectivity in favor of dihydropyran **9** (entries 3, 5 and 6), and we were pleased to observe that using only 1 mol% of Grubbs' catalyst II (**12**), dihydropyran **9** could be obtained in high selectivity (>95:5) in 85% yield (entry 7).



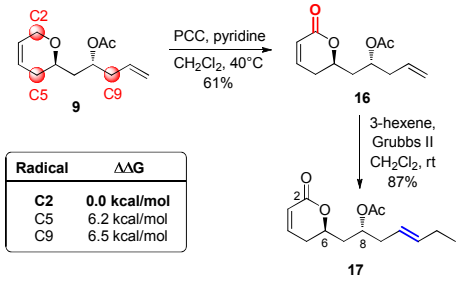

Scheme 3. Synthesis of dihydropyran **9**

The next step was a selective allylic radical-based C-H oxidation at C-2 position of dihydropyran **9** to install the desired lactone. To answer the question whether C-2 would be more easily oxidized than the other two competing allylic positions (C-5 and C-9), we performed DFT calculations using Gaussian 09.[19] The relative C-H bond strength for the three competing radical oxidation reactions were estimated by computing the relative stability of the radical species resulting from homolytic C-H bond clevage at the UB3LYP/6-31+G** level of theory.[20] Our calculations suggested that the radical centered on C-2 would be more stable than those centered on C-5 or C-9 ($\Delta\Delta G$ = 6.2 and 6.5 kcal/mol, respectively). This result encouraged us to pursue our goals, and after several experimentation we found that the use of PCC and pyridine selectively oxidized the C-2 position to furnish the dihydropyranone **16** in 61% yield. The last C-C bond was constructed via a cross-metathesis reaction using symmetric 3-hexene as partner of **16**, the product presented the new double bond with exclusively *E*-selectivity (Scheme 4).

Table 1. Screening of condition for RCM



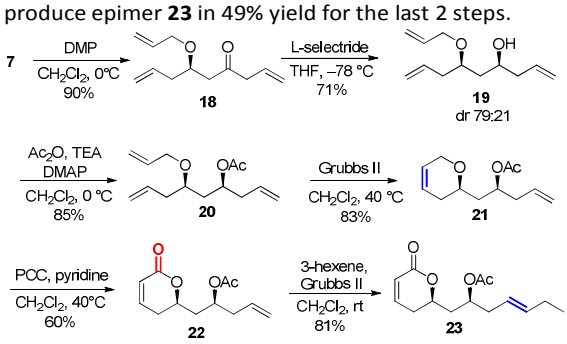

| entry | catalyst | loading | Temperature | ratio 9/10 | yield |
|---|---|---|---|---|---|
| 1 | **11** | 5 mol% | 40 °C | 59:41 | 88% |
| 2 | **11** | 5 mol% | 0 °C | 63:37 | 74% |
| 3 | **13** | 5 mol% | 40 °C | 94:6 | 80% |
| 4 | **14** | 10 mol% | 40 °C | 72:28 | 86% |
| 5 | **15** | 10 mol% | 40 °C | 92:8 | 82% |
| 6 | **12** | 5 mol% | 40 °C | >95:5 | 86% |
| **7** | **12** | **1 mol%** | **40 °C** | **>95:5** | **85%** |




Scheme 4. Synthesis of epimer **17** ($\Delta\Delta G$ values are relative energies of the correspondent allylic radical species)

Synthesis of dihydropyran-2-one **23**, the C-8 epimer of lactone **17**, was conducted in a similar fashion (Scheme 5). Stereogenic center at C-8 was inverted in a sequence of oxidation with Dess-Martin periodinane (DMP) and diastereoselective reduction, to furnish 1,3-*syn* compound as the major isomer (*d.r.* 79:21) in 64% yield (2 steps). Alcohol **19** was acetylated with acetic anhydride, and the resulting triene **20** was used in the optimized conditions for RCM reaction, obtaining the dihydropyran **21** as a single isomer in 71% yield (2 steps). C-H oxidation and cross-metathesis reaction were

performed under similar conditions as previously described, to produce epimer **23** in 49% yield for the last 2 steps.




Scheme 5. Synthesis of epimer **23**

Comparison of the $^{13}C$ NMR spectrum of natural cryptolatifolione and synthetic epimers **17** and **23** made possible the unequivocal assignment of the 1,3-*syn* relationship in the natural product (Figure 1). The $[\alpha]_D$ value of synthetic **23** (+93, c 1.4, $CHCl_3$) is in good agreement with the reported for the natural compound $[\alpha]_D$ (c 1.4, $CHCl_3$) = +97.8.

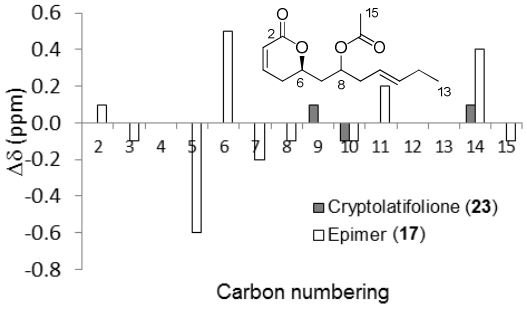



Fig. 1. Comparison of $^{13}C$ NMR data ($\Delta\delta$) of natural Cryptolatifolione and synthetic epimers **17** and **23**.

## Conclusions

In summary, we developed the first total synthesis of Cryptolatifolione (**23**) in 8 steps and 10% overall yield, and its epimer at C-8 in 6 steps and 17% overall yield. The syntheses feature construction of four C-C bonds by catalytic methods, and use of a C-H oxidation to install the carbonyl group in a protecting-group-free fashion.

## Experimental section

### General

Starting materials and reagents were obtained from commercial sources and used as received unless otherwise specified. Dichloromethane, triethylamine and *N*,*N*-diisopropylethylamine were treated with calcium hydride and distilled before use. Tetrahydrofuran and 1,4-dioxane were treated with metallic sodium and benzophenone and distilled before use. Anhydrous dimethylformamide and pyridine were obtained from Aldrich. Anhydrous reactions were carried out with continuous stirring under atmosphere of dry nitrogen. Progress of the reactions was monitored by thin-layer chromatography (TLC) analysis (Merck, silica gel 60 F254 on aluminum plates). $^1H$ NMR and $^{13}C$ NMR were recorded on Bruker 250, 500 or 600, the chemical shifts (δ) were reported in parts per million (ppm) relative to deuterated solvent as the internal standard ($CDCl_3$ 7.26 ppm, 77.0 ppm), coupling constants (*J*) are in hertz (Hz). Mass spectra were recorded on a Waters Xevo Q-Tof apparatus operating in electrospray mode (ES). Infrared spectra with Fourier transform (FTIR) were recorded on a Therm Scientific Nicolet iS5, the principal absorptions are listed in $cm^{-1}$. The values of optical rotation were measured at 25 °C in a polarimeter Perkin–Elmer 341, with sodium lamp, the measure is described as follow $[\alpha]_D^T$ (*c* (g/100 mL), solvent). IUPAC names of the compounds were generated using ChemBioDraw Ultra 13.0. HPLC analyses were carried out using Waters 2695 Alliance® equipment, all experiments were realized at room temperature with a photodiode array detector. GC analyses were performed on Agilent 6890 Series instrument equipped with FID detector. NMR spectra were processed using ACD/NMR Processor Academic Edition version 12.01.

**(4*R*,6*R*)-nona-1,8-diene-4,6-diol (2)**. A pressure tube was charged with $[Ir(cod)Cl_2]$ (104 mg, 0.15 mmol, 5 mol%), $Cs_2CO_3$ (393 mg, 1.20 mmol, 40 mol%), 4-chloro-3-nitrobenzoic acid (121 mg, 0.60 mmol, 20 mol%) and (*R*)-BINAP (189 mg, 0.30 mmol, 10 mol%). The tube was purged with nitrogen, and dry 1,4-dioxane (15 mL) was added followed by allyl acetate (3.3 mL, 30 mmol, 10 eq.), the pressure tube was sealed and heated at 90 °C for 30 min. The mixture was cooled to rt, then a solution of 1,3-propanediol (231 mg, 3.00 mmol, 1 eq.) in 1,4-dioxane (15 mL) was added to the reaction, which was heated at 90°C for 3.5 days. The solvent was evaporated *in vacuo*, and the brown residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 75:25 to 60:40) to give the diol **2** (281 mg, 1.80 mmol) as anyellowish oil in 60% yield. TLC ($SiO_2$): $R_f$ = 0.30 (hexanes:EtOAc 60:40).$[\alpha]_D^{25}$ = –30 (*c* 1.0, $CHCl_3$), for *ent*-diol: $[\alpha]_{D,lit}$ = +35 (*c* 1.0, $CHCl_3$).[22] $^1H$ NMR (250 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.7, 9.8, 7.1 Hz, 2H), 5.16-5.02 (m, 4H), 3.97 (quint., *J* = 5.8 Hz, 2H), 3.06 (br. s, 2H), 2.25 (t, *J* = 6.6 Hz, 4H), 1.61 (t, *J* = 5.8 Hz, 2H). $^{13}C$ NMR (62.9 MHz, $CDCl_3$): δ 134.8 (2CH), 118.1 ($2CH_2$), 68.2 (2CH), 42.1 ($2CH_2$), 41.6 ($CH_2$). *d.r.*> 20:1, *e.e.*> 99%.

**(4*R*,6*R*)-6-((4-methoxybenzyl)oxy)nona-1,8-dien-4-ol (3)**. NaH (42 mg, 1.1 mmol, 1.1 eq., 60% in mineral oil) and TBAI (36 mg, 0.096 mmol, 0.1 eq.) were added to a solution of diol **2** (150 mg, 0.96 mmol, 1 eq.) in dry DMF (5 mL) at rt. After 10 min, PMBCl (146 μL, 1.1 mmol, 1.1 eq.) was added, and the reaction was stirred for 18 h. Water (50 mL) was added to the reaction, and the mixture was extracted with ether (3 x 50 mL), then the organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 75:25) to give the alcohol **3** (188 mg, 0.68 mmol) as a colorless oil in 71% yield. TLC ($SiO_2$): $R_f$ = 0.43 (hexanes:EtOAc 75:25).$[\alpha]_D^{25}$ = –52 (*c* 1.0, $CHCl_3$).$^1H$ NMR (250 MHz, $CDCl_3$): δ 7.31-7.22 (m, 2H), 6.91-6.83 (m, 2H), 5.82 (ddt, *J* = 17.7, 9.7, 7.1 Hz, 1H), 5.80 (ddt, *J* = 17.2, 9.9, 7.1 Hz, 2H), 5.16-5.02 (m, 4H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 3.93 (quint., *J* = 5.9 Hz, 1H), 3.83-

3.71 (m, 1H), 3.79 (s, 3H), 2.58 (br. s, 1H), 2.52-2.28 (m, 2H), 2.25-2.15 (m, 2H), 1.69-1.60 (m, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 159.4 (C), 135.1 (CH), 134.6 (CH), 130.5 (C), 129.6 (2CH), 117.7 ($CH_2$), 117.5 ($CH_2$), 114.0 (2CH), 75.9 (CH), 71.1 ($CH_2$), 67.7 (CH), 55.4 ($CH_3$), 42.3 ($CH_2$), 39.8 ($CH_2$), 38.2 ($CH_2$). IR (NaCl, film): 3441 (broad), 2916, 1514, 1248, 1071, 1036, 914, 820 cm$^{-1}$. HRMS: (ESI) Calculated for $C_{17}H_{24}O_3Na$ $[M+Na]^+$: 299.1618, found: 299.1628.

**(4*R*,6*R*)-6-((4-methoxybenzyl)oxy)nona-1,8-dien-4-yl acrylate (4)**. DIPEA (50 μL, 0.28 mmol, 3 eq.) was added to a solution of alcohol **3** (26 mg, 0.094 mmol, 1 eq.) in dry $CH_2Cl_2$ (7 mL) at 0 °C. After 5 min, acryloyl chloride (16 μL, 0.19 mmol, 2 eq.) was added, and the reaction was stirred for 2 h. Brine (10 mL) was added to the reaction, and the mixture was extracted with $CH_2Cl_2$ (2 x 20 mL), then the organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give the acrylate **4** (29 mg, 0.088 mmol) as a colorless oil in 93% yield. TLC ($SiO_2$): $R_f$ = 0.30 (hexanes:EtOAc 90:10). $[\alpha]_D^{25}$ = −88 (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ 7.32-7.22 (m, 2H), 6.90-6.82 (m, 2H), 6.39 (dd, *J* = 17.2, 1.4 Hz, 1H), 6.10 (dd, *J* = 17.2, 10.3 Hz, 1H), 5.92-5.66 (m, 3H), 5.29 (quint., *J* = 6.3 Hz, 1H), 5.17-5.01 (m, 4H), 4.50 (d, *J* = 10.6 Hz, 1H), 4.32 (d, *J* = 10.6 Hz, 1H), 3.79 (s, 3H),3.54-3.42 (m, 1H), 2.44-2.26 (m, 4H), 1.78-1.69 (m, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 165.8 (C), 159.3 (C), 134.4 (CH), 133.6 (CH), 130.6 (C), 130.5 ($CH_2$), 129.8 (2CH), 128.9 (CH), 118.0 ($CH_2$), 117.6 ($CH_2$), 113.9 (2CH), 74.6 (CH), 71.3 ($CH_2$), 70.7 (CH), 55.4 ($CH_3$), 39.5 ($CH_2$), 38.9 ($CH_2$), 38.5 ($CH_2$). IR (NaCl, film): 2917, 1720, 1636, 1514, 1405, 1193, 1037, 990 cm$^{-1}$. HRMS: (ESI) Calculated for $C_{20}H_{26}O_4Na$ $[M+Na]^+$: 353.1723, found: 325.1724.

**(1*R*,6*R*)-6-((4-methoxybenzyl)oxy)cyclohept-3-en-1-yl acrylate (5)**. Grubbs' catalyst 1$^{st}$ generation (7.0 mg, 8.2 μmol, 10 mol%) was added to a solution of acrylate **4** (27.1 mg, 82 μmol, 1 eq.) in $CH_2Cl_2$ (16 mL) at 40 °C. After 90 min, the solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give the acrylate **5** (22.7 mg, 75 μmol) as a brownish oil in 92% yield. TLC ($SiO_2$): $R_f$ = 0.20 (hexanes:EtOAc 90:10). $[\alpha]_D^{25}$ = −30 (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ7.30-7.22 (m, 2H), 6.90-6.82 (m, 2H), 6.37 (dd, *J* = 17.4, 1.7 Hz, 1H), 6.08 (dd, *J* = 17.2, 10.3 Hz, 1H), 5.85-5.65 (m, 3H), 5.18 (tt,*J* = 7.7, 3.8 Hz,1H), 4.47 (s, 2H), 3.79 (s, 3H), 3.74-3.65 (m, 1H), 2.50-2.37 (m, 4H), 2.25-2.12 (m, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 165.5 (C), 159.2 (C), 130.8 (C), 130.5 ($CH_2$), 129.3 (2CH), 129.0 (CH), 128.6 (CH), 127.1 (CH), 113.9 (2CH), 72.1 (CH), 69.9 ($CH_2$), 69.3 (CH), 55.4 ($CH_3$), 41.4 ($CH_2$), 33.7 ($CH_2$), 33.3 ($CH_2$). IR (NaCl, film): 2935, 1719, 1513, 1195, 1076, 1048, 754 cm$^{-1}$. HRMS: (ESI) Calculated for $C_{18}H_{22}O_4Na$ $[M+Na]^+$: 325.1410, found: 325.1410.

**(4*R*,6*R*)-6-(allyloxy)nona-1,8-dien-4-ol (7)**. NaH (360 mg, 9 mmol, 2 eq., 60% in mineral oil) was added to a solution of diol **2** (703 mg, 4.5 mmol, 1 eq.) in dry DMF (20 mL) at rt. After 10 min, allyl bromide (482 μL, 5.4 mmol, 1.2 eq.) was added, and the reaction was stirred for 30min. Water (100 mL) was added to the reaction, and the mixture was extracted with ether (3 x 50 mL), then the organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10 to 75:25) to give the alcohol **7** (662 mg, 3.4 mmol) as a colorless oil in 75% yield. TLC ($SiO_2$): $R_f$ = 0.50 (hexanes:EtOAc 75:25). $[\alpha]_D^{25}$ = −46 (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ5.96-5.66 (m, 3H), 5.28-5.00 (m, 6H), 4.07 (ddt, *J* = 12.6, 5.5, 1.4 Hz, 1H), 3.96 (ddt, *J* = 12.6, 5.7, 1.3 Hz, 1H), 3.96-3.94 (m, 1H), 3.72-3.63 (m, 1H), 2.75 (br. s, 1H), 2.45-2.15 (m, 4H), 1.63-1.56 (m, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 135.0 (CH), 134.9 (CH), 134.4 (CH), 117.6 ($CH_2$), 117.4 ($CH_2$), 116.9 ($CH_2$), 76.3 (CH), 70.3 ($CH_2$), 67.6 (CH), 42.3 ($CH_2$), 39.7 ($CH_2$), 38.2 ($CH_2$). IR (NaCl, film): 3388 (broad), 2978, 2918, 1073, 995, 914 cm$^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{20}O_2Na$ $[M+Na]^+$: 219.1356, found: 219.1368.

**(4*R*,6*R*)-6-(allyloxy)nona-1,8-dien-4-yl acetate (8)**. Triethylamine (619 μL, 4.4 mmol, 5 eq.) and DMAP (22 mg, 0.18 mmol, 0.2 eq) were added to a solution of alcohol **7** (173 mg, 0.88 mmol, 1 eq.) in dry $CH_2Cl_2$ (15 mL) at 0 °C. After 5 min, acetic anhydride (214 μL, 2.2 mmol, 2.5 eq.) was added, and the reaction was stirred for 2 h. Brine (20 mL) was added to the reaction, and the mixture was extracted with $CH_2Cl_2$ (2 x 20 mL), then the organic phases were combined, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give acetate **8** (172 mg, 0.72 mmol) as a colorless oil in 82% yield. TLC ($SiO_2$): $R_f$ = 0.41 (hexanes:EtOAc 90:10). $[\alpha]_D^{25}$ = −75 (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ 5.96-5.64 (m, 3H), 5.28-4.98 (m, 7H), 4.03 (dd, *J* = 12.3, 5.5 Hz, 1H), 3.87 (dd, *J* = 12.3, 6.0 Hz, 1H), 3.38 (quint., *J* = 5.7 Hz, 1H), 2.38-2.20 (m, 4H), 2.01 (s, 3H), 1.70-1.60 (m, 2H).$^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.5 (C), 135.1 (CH), 134.2 (CH), 133.5 (CH), 117.8 ($CH_2$), 117.4 ($CH_2$), 116.9 ($CH_2$), 74.7 (CH), 70.5 ($CH_2$), 70.3 (CH), 39.3 ($CH_2$), 38.6 ($CH_2$), 38.5 ($CH_2$), 21.2 ($CH_3$). IR (NaCl, film): 2917, 2849, 1739, 1374, 1238, 1081, 917 cm$^{-1}$. HRMS: (ESI) Calculated for $C_{14}H_{22}O_3Na$ $[M+Na]^+$: 261.1461, found: 261.1464.

**(*R*)-1-((*R*)-3,6-dihydro-2*H*-pyran-2-yl)pent-4-en-2-yl acetate (9)**. Grubbs' catalyst 2$^{nd}$ generation (5 mg, 6 μmol, 1 mol%) was added to a solution of allyl ether **8** (143 mg, 0.60 mmol, 1 eq.) in $CH_2Cl_2$ (120 mL) at 40 °C. After 60 min, the solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give the dihydropyran **9** (108 mg, 0.51 mmol) as a brownish oil in 85% yield. TLC ($SiO_2$): $R_f$ = 0.37 (hexanes:EtOAc 90:10). $[\alpha]_D^{25}$ = −5 (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ5.85-5.67 (m, 3H), 5.26-5.03 (m, 3H), 4.23-4.03 (m, 2H), 3.48 (tt, *J* = 8.8, 4.1 Hz, 1H), 2.40-2.25 (m, 2H), 2.10-1.90 (m, 2H), 2.03 (s, 3H), 1.75-1.65 (m, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ170.6 (C), 133.5 (CH), 126.5 (CH), 124.0 (CH), 117.8 ($CH_2$), 70.2 (CH), 70.1 (CH), 65.9 ($CH_2$),40.1 ($CH_2$), 39.3 ($CH_2$), 31.3 ($CH_2$), 21.2 ($CH_3$). IR (NaCl, film): 2917, 1738, 1383, 1241, 1091, 918 cm$^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{18}O_3Na$ $[M+Na]^+$: 233.1148, found: 233.1168.

**(*R*)-1-((*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)pent-4-en-2-yl acetate (16)**. PCC (291 mg, 1.35 mmol, 3 eq.) and pyridine (219 μL, 2.7 mmol, 6 eq.) were added to a solution of dihydropyran **9** (94.6 mg, 0.45 mmol, 1 eq.) in $CH_2Cl_2$ (20 mL) at 40 °C. After

12 h, a second portion of PCC (291 mg, 1.35 mmol, 3 eq.) was added to the mixture. After a second period of 12 h, the mixture was filtered through a double layered plug containing celite and silica, the plug was flushed with EtOAc. The solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 75:25) to give the dihydropyranone **16** (62 mg, 0.28 mmol) as a colorless oil in 61% yield. TLC ($SiO_2$): $R_f$ = 0.15 (hexanes:EtOAc 75:25). $[\alpha]_D^{25}$ = +22 (*c*1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ 6.86 (dt, *J* = 9.6, 4.1 Hz, 1H), 6.02 (dt, *J* = 9.9, 1.7 Hz, 1H), 5.74 (ddt, *J* = 17.4, 9.8, 7.1Hz,1H), 5.23-5.05 (m, 3H), 4.56-4.44 (m, 1H), 2.42-2.28 (m, 4H), 2.10-1.98 (m, 1H),2.04 (s, 3H), 1.85 (ddd, *J* = 14.8, 9.2, 3.6 Hz, 1H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.2 (C), 163.7 (C), 144.7 (CH), 132.8 (CH), 121.3 (CH), 118.3 ($CH_2$), 74.5 (CH), 69.4 (CH), 38.8 ($2CH_2$), 29.5 ($CH_2$), 21.0 ($CH_3$). IR (NaCl, film): 2919, 1727, 1384, 1237, 1040, 819 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{16}O_4Na$ $[M+Na]^+$: 247.0941, found: 247.0935.

**8-*epi*-Cryptolatifolione (17)**. Grubbs' catalyst 2$^{nd}$ generation (7.6 mg, 9 μmol, 10 mol%) was added to a solution of alkene **16** (20.2 mg, 90 μmol, 1 eq.) and *trans*-3-hexene (192 μL, 1.53 mmol, 17 eq.) in $CH_2Cl_2$ (0.9 mL) at rt. After 1h, the solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 75:25) to give 7-*epi*-cryptolatifolione (**17**, 19.8 mg, 78 μmol) as a colorless oil in 87% yield. TLC ($SiO_2$): $R_f$ = 0.20 (hexanes:EtOAc 75:25). $[\alpha]_D^{25}$ = +21 (*c* 1.4, $CHCl_3$). $^1$H NMR (600 MHz, $CDCl_3$): δ 6.85 (ddd, *J* = 9.8, 5.3, 3.2 Hz, 1H), 6.00 (ddd, *J* = 9.8, 2.1, 1.3 Hz, 1H), 5.55-5.49 (m, 1H), 5.34-5.28 (m, 1H), 5.12-5.07 (m, 1H), 4.50-4.44 (m, 1H), 2.36-2.27 (m, 4H), 2.06-1.96 (m, 2H), 2.02 (s, 3H), 1.82 (ddd, *J* = 14.9, 9.4, 3.8 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ170.3 (C), 163.9 (C), 144.7 (CH), 136.2 (CH), 123.0 (CH), 121.5 (CH), 74.7 (CH), 70.1 (CH), 38.9 ($CH_2$), 37.7 ($CH_2$), 29.6 ($CH_2$), 25.6 ($CH_2$), 21.1 ($CH_3$), 13.7 ($CH_3$). IR (NaCl, film): 2963, 2923, 1737, 1383, 1240, 1041, 820 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{14}H_{20}O_4Na$ $[M+Na]^+$: 275.1254, found: 275.1261.

**(*R*)-6-(allyloxy)nona-1,8-dien-4-one (18)**. Dess-Martin periodinane (267 mg, 0.61 mmol, 1 eq.) was added to a solution of alcohol **7** (120 mg, 0.61 mmol, 1 eq.) in $CH_2Cl_2$ (6 mL) at 0 °C. The reaction was stirred at 0 °C for 2 h, then solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 95:5) to give ketone **18** (107 mg, 0.55 mmol) as a colorless oil in 90% yield. TLC ($SiO_2$): $R_f$ = 0.35 (hexanes:EtOAc 90:10). $[\alpha]_D^{25}$ = −52 (*c* 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$): δ 5.99-5.68 (m, 3H), 5.27-5.03 (m, 6H), 4.08-3.86 (m, 3H), 3.19 (d,*J* = 7.0 Hz,2H), 2.69 (dd,*J* = 16.3, 7.7 Hz,1H), 2.49 (d,*J* = 16.1, 4.7 Hz,1H), 2.39-2.19 (m, 2H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 207.2 (C), 134.8 (CH), 133.9 (CH), 130.3 (CH), 118.9 ($CH_2$), 117.8 ($CH_2$), 116.8 ($CH_2$), 74.6 (CH), 70.4 ($CH_2$), 48.7 ($CH_2$), 46.7 ($CH_2$), 38.4 ($CH_2$). IR (NaCl, film): 3079, 2980, 2916, 1716, 1641, 1076, 919 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{18}O_2Na$ $[M+Na]^+$: 217.1199, found: 217.1207.

**(4*S*,6*R*)-6-(allyloxy)nona-1,8-dien-4-ol (19)**. A solution of L-selectride in THF (1 M, 1.6 mL, 1.6 mmol, 3 eq.) was added to a solution of ketone **18** (103 mg, 0.53 mmol, 1 eq.) in THF (11 mL) at −78 °C and the mixture was stirred for 3h at the same temperature. An aqueous solution of HCl (1 M, 20 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were combined, dried ($Na_2SO_4$), and concentrated. The residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give alcohol **19** (74 mg, 0.38 mmol) as a colorless oil in 71% yield. The purified product contains the minor diastereoisomer **7**. TLC ($SiO_2$): $R_f$ = 0.50 (hexanes:EtOAc 75:25). $[\alpha]_D^{25}$ = −56 (*c* 1.0, $CHCl_3$). Major isomer: $^1$H NMR (250 MHz, $CDCl_3$): δ 5.97-5.65 (m, 3H), 5.29-5.00 (m, 6H), 4.18-4.05 (m, 1H), 4.02-3.76 (m, 2H), 3.71-3.59 (m, 1H), 3.16 (br. s, 1H), 2.41-2.13 (m, 4H), 1.68-1.53 (m, 2H). Major isomer: $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 134.8 (CH), 134.3 (CH), 133.7 (CH), 117.6 ($CH_2$), 117.25 ($CH_2$), 117.20 ($CH_2$), 79.1 (CH), 70.8 (CH), 69.6 ($CH_2$), 42.0 ($CH_2$), 40.0 ($CH_2$), 38.0 ($CH_2$). IR (NaCl, film): 3426 (broad), 3077, 2921, 2859, 1641, 1074, 996, 915 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{20}O_2Na$ $[M+Na]^+$: 219.1356, found: 219.1355. *d.r.* = 79:21.

**(4*S*,6*R*)-6-(allyloxy)nona-1,8-dien-4-yl acetate (20)**. Triethylamine (239 μL, 1.7 mmol, 5 eq.) and DMAP (8.4 mg, 69 μmol, 0.2 eq) were added to a solution of alcohol **19** (66.7 mg, 0.34 mmol, 1 eq.) in dry $CH_2Cl_2$ (16 mL) at 0 °C. After 5 min, acetic anhydride (83 μL, 0.85 mmol, 2.5 eq.) was added, and the reaction was stirred for 2 h. Brine (20 mL) was added to the reaction, and the mixture was extracted with $CH_2Cl_2$ (2 x 20 mL), then the organic phases were combined, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give acetate **20** (68.7 mg, 0.29 mmol) as a colorless oil in 85% yield. The purified product contains the minor diastereoisomer **8**. TLC ($SiO_2$): $R_f$ = 0.41 (hexanes:EtOAc 90:10). $[\alpha]_D^{25}$ = −14 (*c* 1.0, $CHCl_3$). Major isomer: $^1$H NMR (250 MHz, $CDCl_3$): δ 5.96-5.62 (m, 3H), 5.28-5.00 (m, 7H), 4.07-3.82 (m, 2H), 3.42 (quint., *J* = 6.0 Hz, 1H), 2.36-2.20 (m, 4H), 1.99 (s, 3H), 1.88-1.61 (m, 2H). Major isomer: $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.4 (C), 135.0 (CH), 134.1 (CH), 133.4 (CH), 117.8 ($CH_2$), 117.3 ($CH_2$), 116.6 ($CH_2$), 75.4 (CH), 70.7 (CH), 69.5 ($CH_2$), 38.8 ($CH_2$), 37.8 ($CH_2$), 37.5 ($CH_2$), 21.1 ($CH_3$). IR (NaCl, film): 3079, 2979, 2921, 1738, 1384, 1239, 1079, 917 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{14}H_{22}O_3Na$ $[M+Na]^+$: 261.1461, found: 261.1466.

**(*S*)-1-((*R*)-3,6-dihydro-2*H*-pyran-2-yl)pent-4-en-2-yl acetate (21)**. Grubbs' catalyst 2$^{nd}$ generation (2.4 mg, 2.8 μmol, 1 mol%) was added to a solution of allyl ether **20** (66.7 mg, 0.28 mmol, 1 eq.) in $CH_2Cl_2$ (30 mL) at 40 °C. After 30 min, the solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 90:10) to give the dihydropyran **21** (49 mg, 0.23 mmol) as a brownish oil in 83% yield. The purified product contains the minor diastereoisomer **9**. TLC ($SiO_2$): $R_f$ = 0.37 (hexanes:EtOAc 90:10) $[\alpha]_D^{25}$ = +65 (*c* 1.0, $CHCl_3$). Major isomer: $^1$H NMR (250 MHz, $CDCl_3$): δ 5.83-5.64 (m, 3H), 5.20-5.01 (m, 3H), 4.15-4.08 (m, 2H), 3.64-3.42 (m, 1H), 2.40-2.25 (m, 2H), 2.05-1.80 (m, 3H),2.00 (s, 3H), 1.72-1.58 (m, 1H). Major isomer: $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.6 (C), 133.5 (CH), 126.2 (CH), 123.8 (CH), 117.8 ($CH_2$), 70.7 (CH), 70.5 (CH), 65.6 ($CH_2$), 39.6 ($CH_2$), 38.7 ($CH_2$), 30.9 ($CH_2$), 21.2 ($CH_3$). IR (NaCl, film): 2921, 1735, 1384, 1242, 1090, 1023, 918 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{18}O_3Na$ $[M+Na]^+$: 233.1148, found: 233.1147.

**(*S*)-1-((*R*)-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)pent-4-en-2-yl acetate (22)**. PCC (149 mg, 0.69 mmol, 3 eq.) and pyridine (112 μL, 1.38 mmol, 6 eq.) were added to a solution of dihydropyran **21** (48.4 mg, 0.23 mmol, 1 eq.) in $CH_2Cl_2$ (10 mL) at 40 °C. After 12 h, a second portion of PCC (149 mg, 0.69 mmol, 3 eq.) was added to the mixture. After a second period of 12 h, the mixture was filtered through a double layered plug containing celite and silica, the plug was flushed with EtOAc. Solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 75:25) to give the dihydropyranone **22** (31 mg, 0.14 mmol) as a colorless oil in 60% yield. The purified product contains a single diastereoisomer. TLC ($SiO_2$): $R_f$ = 0.18 (hexanes:EtOAc 75:25). $[\alpha]_D^{25}$ = +89 (*c* 0.56, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ 6.86 (ddd, *J* = 9.8, 6.1, 2.4 Hz, 1H), 6.02 (dd, *J* = 9.6, 1.8 Hz, 1H), 5.73 (ddt, *J* = 17.1, 10.2, 7.0 Hz,1H), 5.14-5.06 (m, 3H), 4.53-4.45 (m, 1H), 2.51-2.43 (m, 1H), 2.40-2.35 (m, 2H), 2.34-2.25 (m, 1H), 2.16 (ddd, *J* = 14.8, 9.0, 6.1 Hz, 1H), 2.06 (s, 3H), 1.89 (ddd, *J* = 14.5, 7.2, 3.8 Hz, 1H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.7 (C), 163.9 (C), 144.7 (CH), 132.8 (CH), 121.4 (CH), 118.5 ($CH_2$), 75.0 (CH), 69.5 (CH), 38.8 ($CH_2$), 38.7 ($CH_2$), 29.1 ($CH_2$), 21.1 ($CH_3$). IR (NaCl, film): 2957, 2917, 1733, 1384, 1239, 1041 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{12}H_{16}O_4Na$ $[M+Na]^+$: 247.0941, found: 247.0946.

**Cryptolatifolione (23)**. Grubbs' catalyst 2$^{nd}$ generation (8.1 mg, 9.5 μmol, 10 mol%) was added to a solution of alkene **22** (21.3 mg, 95 μmol, 1 eq.) and *trans*-3-hexene(203 μL, 1.62 mmol, 17 eq.) in $CH_2Cl_2$ (1.4 mL) at rt. After 1 h, the solvent was removed *in vacuo*, and the residue was subjected to flash chromatography ($SiO_2$, hexanes:EtOAc, 75:25) to give cryptolatifolione (**23**, 19.4 mg, 77 μmol) as a colorless oil in 81% yield. TLC ($SiO_2$): $R_f$ = 0.61 (hexanes:EtOAc 50:50). $[\alpha]_D^{25}$ = +93 (*c* 1.4, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$): δ 6.85 (ddd, *J* = 9.8, 6.1, 2.1 Hz, 1H), 6.00 (dd, *J* = 9.6, 2.1 Hz, 1H), 5.58-5.50 (m, 1H), 5.35-5.27 (m, 1H), 5.06-4.99 (m, 1H), 4.51-4.44 (m, 1H), 2.51-2.43 (m, 1H), 2.33-2.23 (m, 3H), 2.13 (ddd, *J* = 14.8, 9.3, 6.0 Hz, 1H), 2.04 (s, 3H), 2.00 (quint., *J* = 7.2 Hz, 2H), 1.88 (ddd, *J* = 14.5, 7.3, 3.7 Hz, 1H), 0.95 (t, *J* = 7.5 Hz, 3H). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ 170.7 (C), 164.0 (C), 144.7 (CH), 136.4 (CH), 122.9 (CH), 121.4 (CH), 75.2 (CH), 70.0 (CH), 38.7 ($CH_2$), 37.7 ($CH_2$), 29.1 ($CH_2$), 25.6 ($CH_2$), 21.1 ($CH_3$), 13.7 ($CH_3$). IR (NaCl, film): 2963, 2932, 1734, 1384, 1241, 1039, 970, 821 $cm^{-1}$. HRMS: (ESI) Calculated for $C_{14}H_{21}O_4$ $[M+H]^+$: 253.1434, found: 253.1434.

## Acknowledgements

The authors thank Dr. Rodrigo V. Pirovani and Dr. Carolina M. Avila for helpful discussions, and Prof. Dr. Marcos N. Eberlin, Prof. Dr. Fábio C. Gozzo and Hugo C. R. de Jesus for HRMS analyses. This work was made possible by grants from FAPESP (proc. #09/51602-5) and CNPq (L.F.T.N., proc. #131015/2014-1).

## Notes and references

1 Tunac, J. B.; Graham, B. D.; Dobson, W. E. *J. Antibiot.* **1983**, *36*, 1595.
2 Sirirath, S.; Tanaka, J.; Ohtani, I. I.; Ichiba, T.; Rachmat, R.; Ueda, K.; Usui, T.; Osada, H.; Higa, T. *J. Nat. Prod.* **2002**, *65*, 1820.
3 Cavalheiro, A. J.; Yoshida, M. *Phytochemistry* **2000**, *53*, 811.
4 De Fátima, A.; Kohn, L. K.; de Carvalho, J. E.; Pilli, R. A. *Bioorg. Med. Chem.* **2006**, *14*, 622.
5 Al Momani, F.; Alkofahi, A. S.; Mhaidat, N. M. *Molecules* **2011**, *16*, 4560.
6 Cardona, W.; Quiñones, W.; Echeverri, F. *Molecules* **2004**, *9*, 666.
7 Jaiswal, M.; Mishra, R.; Mishra, B.; Moorthy, N. S. H. N. *Asian J. Chem.* **2007**, *19*, 4110.
8 Li, H.; Tatlock, J.; Linton, A.; Gonzalez, J.; Jewell, T.; Patel, L.; Ludlum, S.; Drowns, M.; Rahavendran, S. V.; Skor, H.; Hunter, R.; Shi, S. T.; Herlihy, K. J.; Parge, H.; Hickey, M.; Yu, X.; Chau, F.; Nonomiya, J.; Lewis, C. *J. Med. Chem.* **2009**, *52*, 1255.
9 Wanga, J.; Zhao, B.; Zhang, W.; Wu, X.; Wang, R.; Huang, Y.; Chen, D.; Park, K.; Weimer, B. C.; Shen, Y. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7054.
10 De Souza, L. C.; dos Santos, A. F.; Sant'Ana, A. E. G.; Imbroisi, D. O. *Bioorg. Med. Chem.* **2004**, *12*, 865.
11 Marco, J. A.; Carda, M. Recent Advances in the Field of Naturally Occuring 5,6-Dihydropyran-2-ones. In *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*, 1$^{st}$ ed. Tomasz Janecki; Wiley-VCH: Germany, 2013; 51.
12 Carneiro, V. M. T.; Avila, C. M.; Balunas, M. J.; Gerwick, W. H.; Pilli, R. A. *J. Org. Chem.* **2014**, *79*, 630.
13 Novaes, L. F. T.; Drekener, R. L.; Avila, C. M.; Pilli, R. A. *Tetrahedron* **2014**, *70*, 6467.
14 Drewes, S. E.; Horn, M. M.; Wijewardene, C. S. *Phytochemistry* **1996**, *41*, 333. This natural product was christened as cryptolatifolione by the authors of this work.
15 Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5018.
16 *dr* and *ee* of **2** were checked by HPLC of corresponding PMP-acetal, see supporting information for chromatograms.
17 Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357.
18 Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
19 Frisch, M. J. *et al.* Gaussian 09, Revision B.01, Gaussian, Inc.: Wallingford CT, 2009.
20 Wilde, N. C.; Isomura, M.; Mendoza, A.; Baran, P. S. *J. Am. Chem. Soc.***2014**, *136*, 4909.
21 UB3LYP/6-31+G** calculations performed on the three competing allylic radicals derived from **21** again indicated that the radical centered on C-2 would be more stable than those centered on C-5 and C-9 (ΔΔG = 6.4 kcal/mol and 5.6 kcal/mol, respectively).
22 Lu, Y.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 13876-13879.