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Article

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One-step Synthesis of Furan Rings from α-Isopropylidene Ketones Mediated by Iodine/DMSO: An Approach to Potent Bioactive Terpenes

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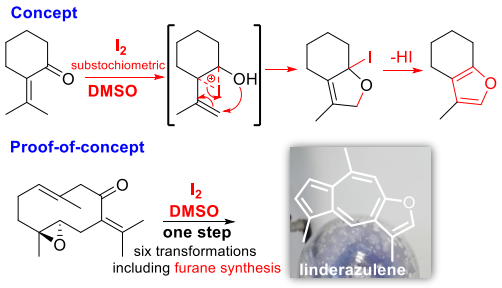
TOC GRAPHIC

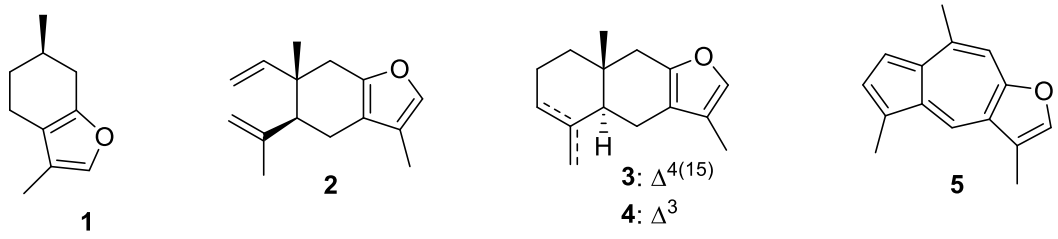


ABSTRACT: The system I_2/DMSO mediates the one-step transformation of α-isopropylidene ketones into furan rings following a biomimetic approach. This methodology has been used for the synthesis of terpene furans such as mintfurane, curzerene, atractylon and isoatractylon, all of them possessing interesting biological activities. The synthesis of linderazulene directly from 4,5-epoxygermacrone via a

cascade reaction shows the potential of this protocol. Additionally, this compound proved to show significant ixodicidal activity.

INTRODUCTION

Terpene furans encompass a number of structures ranging from monoterpenes to tri- or tetraterpenes (carotenes) possessing an interesting variety of biological activities.[1]



Among them, menthofuran (mintfuran) **1** is an aromatic compound present in the essential oil of different peppermint varieties including *Mentha piperita* and pennyroyal (*Mentha pulegium*).[2] Recently, menthofuran was found in red wines, where it is considered the precursor of *p*-menthane lactones, which are an important group of aromatizers.[3] This substance possesses, among other activities, antifungal and hepatotoxic properties.[4] Curzerene **2** was originally isolated from the "curcuma rhizomes", a plant used in traditional Chinese medicine.[5a] It was also found in wild celery (*Smyrnium olusatrum*) and other Smyrnium species.[5b] This was reported to contribute to the antioxidant properties[5c] of the essentials oils of curcuma and to exhibit cytotoxic and antitumor activity.[5b,5d] Atractylon **3** is an eudesmane derivative isolated from the rhizomes of species of Atractylodes.[6a] This furan sesquiterpene presents a wide range of biological activities. Thus, atractylon is the major factor responsible of the anti-inflammatory and antinociceptive effects of *Atractylodes japonica*.[6a] It also shows anti-allergic,[6b] anti-tumor,[6c] anti-viral,[6d] and insecticidal properties.[6e] Its isomer, isoatractylon (**4**), was isolated from the Antarctic gorgonian *Dasystenella acanthine* and was reported to exhibit ichthyotoxicity against the mosquito fish *Gambusia affinis*.[7] Linderazulene (**5**) is a purple pigment isolated from *Paramuricea chamaeleon*[8a] and other gorgonians[8b-d] This compound was reported to be a neoplasm inhibitor, immunomodulator and fungicide.[8e]

The synthesis of menthofuran (**1**) has been previously reported[9] – including a cyclization from pulegone using an aqueous solution of $Ba(OH)_2$ in the presence of a solution of I_2/KI in MeOH.[9b]

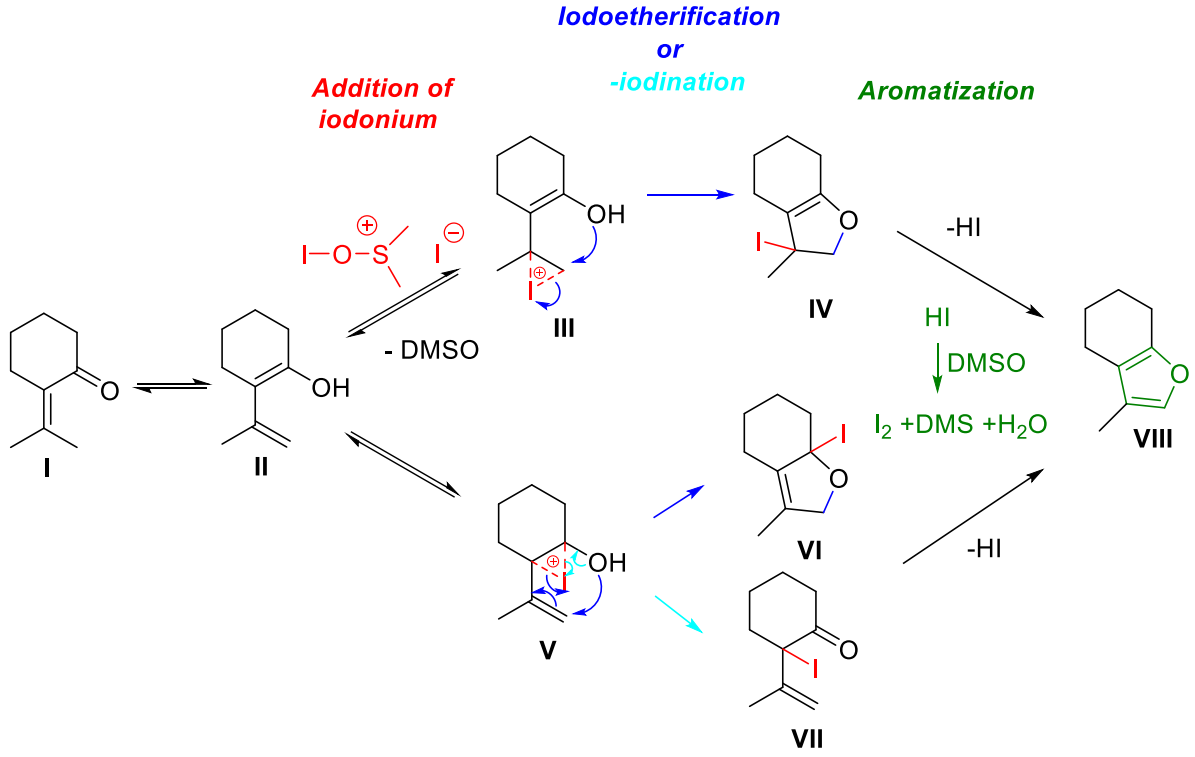
However, few synthetic efforts reporting the synthesis of **2**-**4** were described[10] despite the wide range of biological activities displayed by these compounds.

Molecular iodine is a versatile reagent in organic chemistry[11] mediating a great number of synthetic transformations including some dehydration and dehydrogenative processes. Additionally, the combined use with DMSO not only has increased the range of transformations promoted by I_2 but also made possible its use in catalytic quantities.[12]

It has been reported that in some living organisms terpene furans cooccur with the corresponding derivatives possessing a α-isopropylidene ketone. This moiety was postulated as biogenetic precursor of the furan ring through cytochrome P450 mediated oxidations.[13] Bearing all this in mind, we described an I_2/DMSO mediated synthesis of furans from α-isopropylidene cyclohexanones (**I**), a structural moiety present in different natural products and easily accessible by synthetic means (Scheme 1).

The process would imply the addition of the iodine reagent to enol **II** to produce the cyclic iodonium ions **III** or **V**. Since in the intermediate **II** the two double bonds should be twisted, there should not exist much conjugation between the isopropylidene group and the enol moiety, which would render the intermediate **V** more likely to be formed. Then, intermediates **III** or **V** would evolve, likewise, via an iodoetherification reaction to give the iododihydrofuranes **IV** or **VI**. Finally, an easy HI elimination from intermediates **IV** or **VI** would generate the more stable aromatized structure, **VIII**. Alternatively, intermediate **V** could also produce the α-iodo-β,γ-unsaturated ketone **VII** before evolving to aromatic **VIII**.[14]

Finally, it should be noted that according to the proposed mechanism, the process of regeneration of I_2 by DMSO generates DMS. This sulfide, in the presence of I_2, could generate iododimethylsulfonium iodide,[15] which in turn may contribute to the furan ring synthesis.



Scheme 1. Working Hypothesis: A Simple Process Converting α-Isopropylidene ketones into Furans.

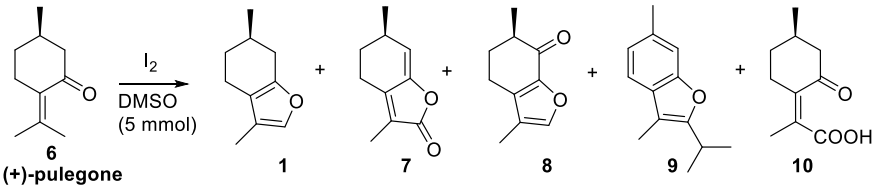
RESULTS AND DISCUSSION

To test the feasibility of this approach to synthesizing furans and explore its applicability to the synthesis of natural bioactive products, we chose commercially available pulegone (**6**) as a model. When pulegone (1 mmol) was exposed to 1 mmol of I_2 and 5 mmol of DMSO in refluxing *tert*-butyl methyl ether (MTBE) for 6 h,[12b] menthofuran (**1**) was obtained in a 15% yield together with minor proportions of dehydromintlactone (**7**) (Table 1, entry 1). The latter product was formed from **1** via an iodation-Korblum oxidation tandem process. This result proved the feasibility of our approach to the synthesis of furans via the cascade of transformations depicted in Scheme 1. If under the same experimental conditions, the reaction time was prolonged to 25 h, only a 2% yield of **1** was obtained but the production of **7** increased up to 35% (Table 1, entry 2). When solvents of medium-low polarity, such as THF, DCM or CCl_4, were tested (Table 1, entries 3-5), mainly degradation of the starting material was obtained when performing the reaction with THF or DCM. However, when CCl_4 was used, noticeable proportions of lactone **7** and ketofuran **8** were obtained. The use of benzene or toluene as solvent (Table 1, entries 6-9) also led to the formation of dehydromintlactone (**7**) as major reaction

product, which implies that the conditions were too harsh to stop the process at the furan level. When hexane was used as solvent, the transformation proceeded more smoothly (Table 1, entries 10-13), and the best yield of **1** (68%) was obtained when the quantity of iodine was reduced to substoichiometric proportions of I_2, that is 0.2 mmol. Noticeably, the use of an excess of I_2 led to a 55% yield of dehydromintlactone **7** (Table 1, entry 13). Gratifyingly, the combined use of I_2 (0.2 mmol) and DMSO as solvent led to a 75% yield of furan **1** (Table 1, entry 14). Additionally, different reactions were achieved using NIS as source of I^+ (Table 1, entries 15-16). Thus, the reaction of 0.2 mmol of NIS with pulegone in DMSO at 50 °C afforded target **1** in 65% yield after 24 h. When toluene was used as solvent and no DMSO was added, the reaction of pulegone with NIS evolved to give the isopropylbenzofurane **9**[16] as the main reaction product, with only traces of **1** being obtained. The formation of **9** implies a retro-Aldol condensation of **1** yielding acetone, which couples with an appropriate furan intermediate.[16]

It should be noted that compounds **7** and **8**, found in some of the abovementioned tests, were also natural products. Thus, dehydromintlactone **7** is claimed to be responsible for the coumarinic odor indicating high-quality in the corresponding peppermint oils.[17] Compound **8** is a minor constituent of *Mentha piperita*.[18]

Table 1. Optimization of the Furan Ring Synthesis of Pulegone



entry	Source of I^+(mmol)	Solvent	Time (h)	1	7	8	9	10
1[a]	1	MTBE	6	15	3	-		
2	1	MTBE	25	t	35	18		14
3	1	THF	2		15			3
4	1	DCM	2		5			
5	1	CCl_4	3		34	32		4
6	1	Toluene	0.5		32	15		5

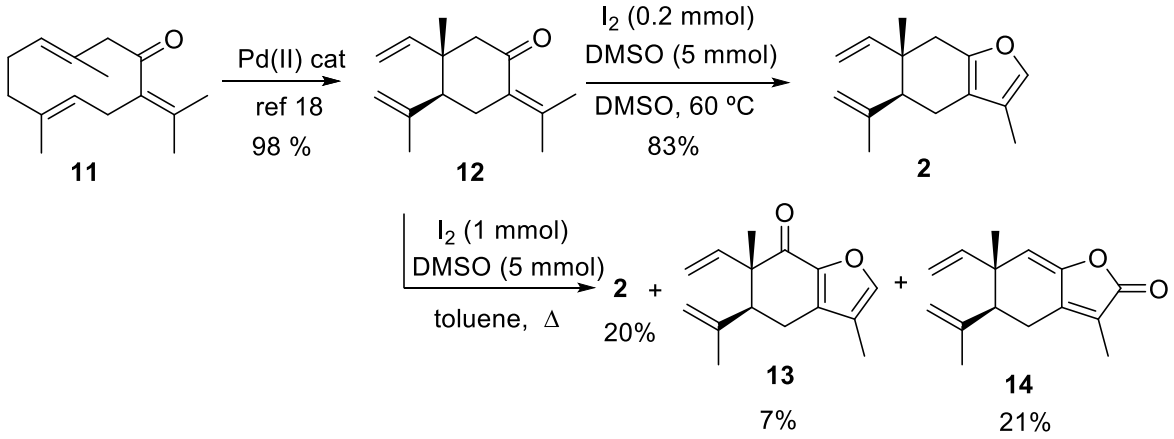
7	0.2	Toluene	0.2		14			4
8	1	Benzene	3		26	19		20
9[b]	0.2	Benzene	1	32	3			
10	1	Hexane	6		44	14		9
11	0.5	Hexane	9	14	29	15		14
12	**0.2**	**Hexane**	12	**68**	2			
13	**3**	**Hexane**	3		**55**	16		4
14[c]	**0.2**	**DMSO**	6.5	**75**				
15[c]	NIS 0.2	DMSO	24	65	3			
16[d]	NIS 0.2	Toluene	0.2	2			52	

The reactions were performed at refluxing temperature and at [C] 0.1 M and using 5 mmol of DMSO to regenerate iodine. [a] 50% of pulegone was recovered. [b] 24% of pulegone was recovered. [c] The reaction was conducted at 60 °C. [d] No DMSO was added.

Once we proved that menthofuran (**1**) can be efficiently synthesized from the corresponding α-isopropylidene cyclohexanone, i.e., pulegone (**6**), we focused our efforts on checking if this methodology is useful to other bioactive furanterpenes, such as natural compounds **2**-**5**. All these compounds were planned to be synthesized using germacrone (**11**) as common starting material. Germacrone is a sustainable natural product, available in multigram scale from cultivated *Geranium macrorrhizum*.[19]

The synthesis of curzerene (**2**) was anticipated to proceed in only two steps from germacrone (Scheme 2). The first step involved the Pd(II)-mediated Cope rearrangement of germacrone to produce elemenone (**12**) in 98% yield.[20]

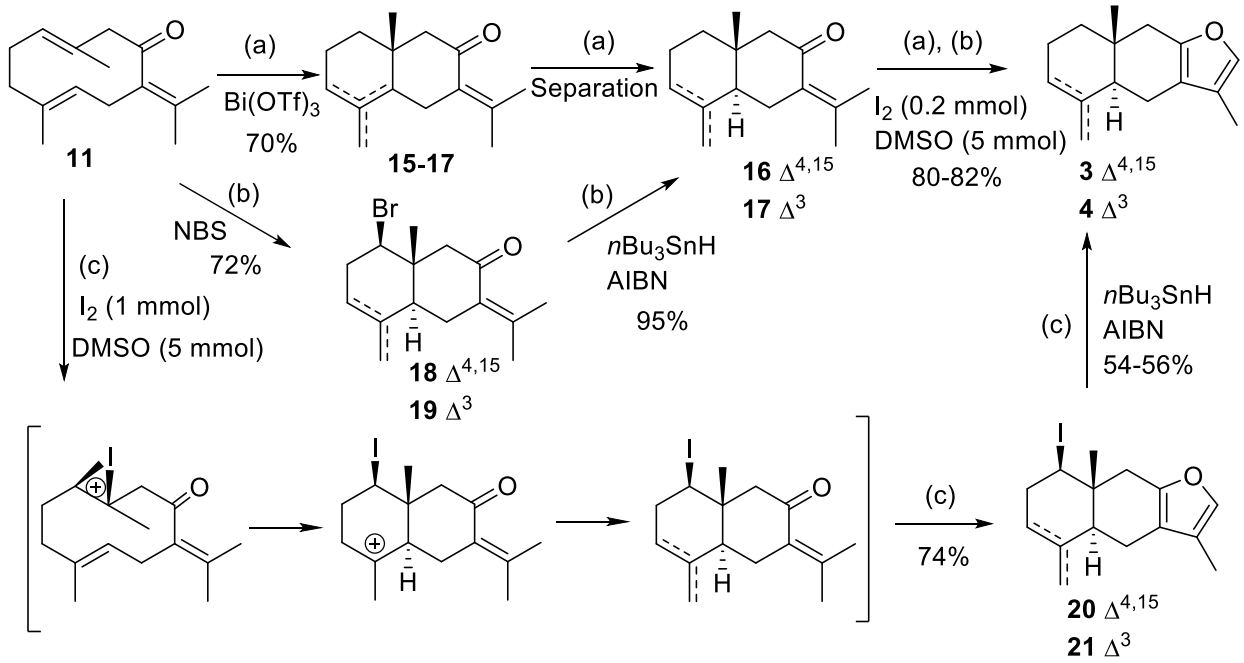
Scheme 2. Synthesis of Curzerene (2)



When elemenone was treated with 0.2 mmol of I_2 in DMSO (the best experimental conditions obtained for menthofuran synthesis), curzerene (**2**) was produced in an excellent (83%) yield. The high chemoselectivity of this transformation warrants mention, since elemenone (**12**) presents two additional double bonds also susceptible of reacting with positive iodine ions (I^+). It should also be noted that when the reaction was performed in refluxing toluene and using 1 mmol of I_2, variable quantities (up to 21%) of the natural elemenolactone curzerenone (**14**) were produced together with minor proportions of the ketocurzerene derivative **13**. Both compounds were previously described from natural sources. Thus, ketone **13** was found in the essential oil of *Asarum caulescens*,[21] whereas lactone **14** was isolated from *Commiphora molmol* (Burseraceae) "Myrrha" and *Curcuma wenyujin* (Zingiberaceae). Compound **14** shows an important cytotoxic activity and anti-inflammatory action comparable to that of hydrocortisone.[22]

Three different synthetic routes to atractylon (**3**) and its isomer **4** were planned (Scheme 3). The first one supposed the initial reaction of germacrone with catalytic $Bi(OTf)_3$ to yield (70%) a mixture of eudesmanes **15**-**17** in a 1:1:0.4 ratio.[23] From this mixture, the *exo* isomer **16** was isolated and tested reaction with the system of I_2/DMSO in different solvents and conditions. Up to 80% yield of atractylon was obtained after refluxing **16** in MTBE for 6 h. The reaction of **17** under the same experimental conditions afforded 82% yield of isoatractylon (**4**).

Scheme 3. Three Routes toward Atractylon (3) and Isoatractylon (4) from Germacrone (11)



In the second route to atractylon, the eudesmane skeleton was generated via electrophilic bromination of germacrone to give the bromoderivatives **18** and **19** in 19 and 53% yield, respectively. The reductive bromination of **18** and **19** proceeded with yields higher that 95% to produce eudesmanes **16** and **17**, which were converted into **3** and **4** following our iodine-mediated protocol for the synthesis of furans.

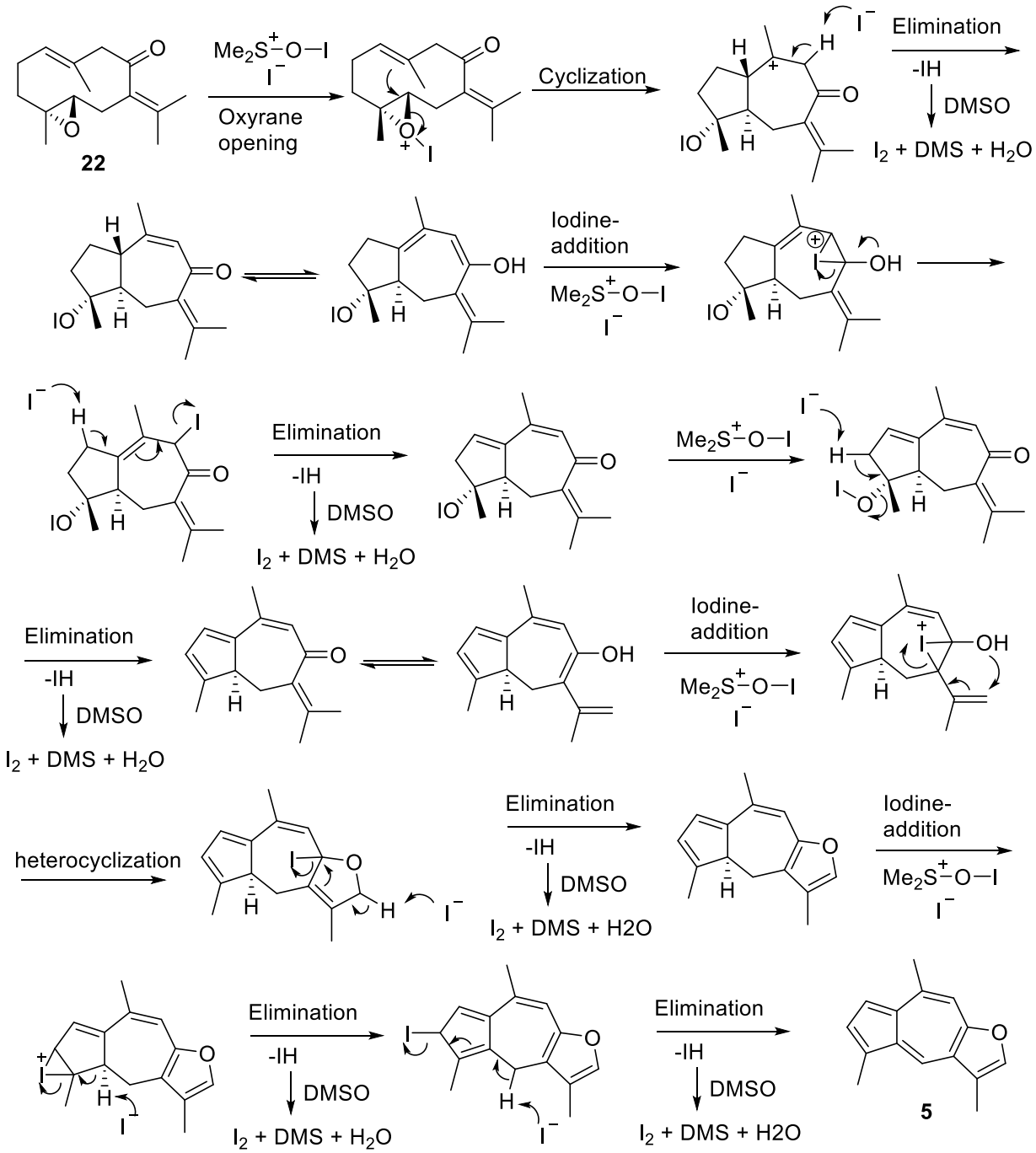
For the third route, we anticipated that the I_2/DMSO system could provoke in only one step the iodocarbocyclization of germacrone to produce iodoeudesmanes that would evolve in the same reaction media to the corresponding iodofurans **20** and **21**. A reductive deiodination in a subsequent step would lead to atractylon (**3**) and its isomer **4**. Thus, when germacrone (**11**) was made to react with the I_2/DMSO system under different experimental conditions, it was found that a 74% of the mixture of iodofurans **20** and **21** (5:1 ratio) were produced if 1 mmol of I_2 and 5 mmol of DMSO were employed, and the reaction was let to evolve for 48 h at rt in hexane. The radical-promoted hydrodeiodination of **20** using the system *n*Bu_3SnH-AIBN afforded a 54% of atractylon (**3**). The same transformation produced a 56% of furan **4** from iododerivative **21**.

At this point, we considered that the different reactivity of the olefin moieties in germacrone (**11**) and elemenone (**12**) (Schemes 2 and 3) warranted rationalization. In this regard, some of us described the two major conformations that germacrone (**11**) presents in solution.[23] These studies revealed that no appreciable conjugation exist between the carbonyl and the isopropylidene groups, thus-preventing the easy formation of the corresponding enol and consequently the generation of the furan ring. Instead, the

reaction took place at the 1,5-diene moiety of germacrone. Once the eudesmane skeleton is generated, the high torsional strain existing in germacrone is released, which favors the formation of the corresponding enols, and therefore, the production of eudesmane furans **20** and **21**. The same reasoning can be argued to rationalize the selective reactivity of elemenone (**12**).

Finally, bearing in mind the synthetic versatility of the I_2/DMSO system,[12] we wondered if I_2/DMSO could promote a cascade reaction to yield linderazulene in only one step from 4,5-epoxygermacrone (**22**), a natural compound that is considered a biosynthetic precursor of guaianes.[24] The process will mimic the natural biosynthesis of linderazulene (**5**) and presents a remarkable synthetic challenge since it would include, in only one step, a series of very different synthetic transformations such as carbocyclization, dehydration, dehydrogenation, heterocyclization and furan aromatization (Scheme 4).

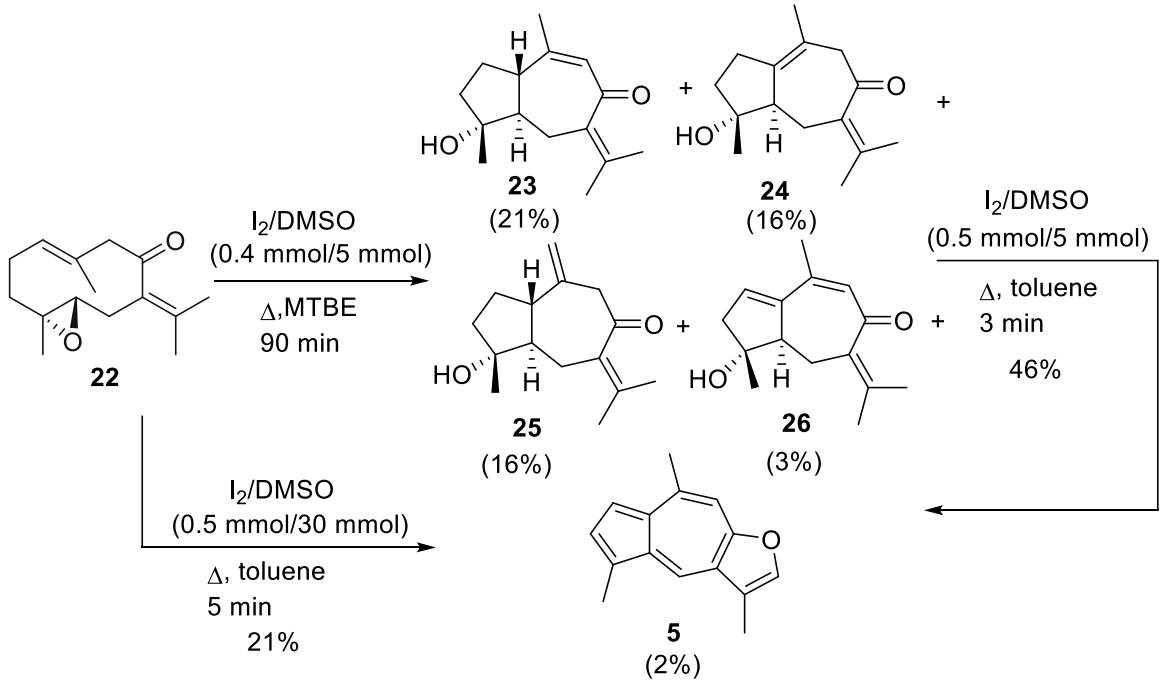
Scheme 4. Proposed Mechanism for the Direct Conversion of 4,5-Epoxygermacrone (22) into Linderazulene (5).



Epoxygermacrone **22** is a natural product present in *Geranium macrorrhizum* and can also be obtained after treatment of germacrone with MCPBA.[23] Initially, **22** was treated with 0.4 mmol of I_2 and 5 mmol of DMSO in refluxing MTBE for 90 min affording a mixture of four guaiane alcohols (**23**-**26**, 5.2:1.9:1.9:1 ratio) together with 2% of linderazulene (**5**) (Scheme 5). The formation of these guaianes confirmed the capability of the I_2/DMSO system of opening epoxides and carrying out carbocyclizations efficiently. Compound **26** is described for the first time, whereas **23**-**25** are active principles of different Curcuma species.[25] With the ultimate idea of improving the efficiency in the generation of linderazulene,

we found that the mixture of guaianes **23**-**25** could be converted into **5** with a 46% yield after treatment with 0.5 mmol of I_2 and 5 mmol of DMSO in refluxing toluene for 3 min. We next focused on optimizing the conditions for the generation of linderazulene in only one step. After examining different conditions, we found that a 21% yield of linderazulene (**5**) was obtained when 0.5 mmol of I_2 and 30 mmol of DMSO were used in refluxing toluene after only 5 min. It should also be underlined that all these transformations were promoted using substoichiometric quantities in iodine. Although the yield obtained is undoubtedly modest, we should take into consideration that this transformation involved seven synthetic steps.

Scheme 5. Conversion of 4,5-Epoxygermacrone (22) into Linderazulene (5).



To conclude, the insecticidal and acaricidal effects of linderazulene against the hard tick *Hyalomma lusitanicum* Koch (Ixodida: Ixodidae) and the insect pests *Spodoptera littoralis* Boisd, *Myzus persicae* Sulz, and *Rhopalosiphum padi* L. Although linderazulene did not present remarkable insecticide activity (Table 2), it showed strong ixodicidal (anti-tick) effects (Table 3).

Table 2. Insecticidal Effects of Linderazulene (5).

Dosis (µg /cm^2)	*S. littoralis*	*M. persicae*	*R. padi*
50	62,48 ± 7,72	43,81 ± 9,67	62,15 ± 6,09

Table 3. Acaricidal Effects of Linderazulene (5).

	mg/ml					
	10	**5**	**2.5**	**1.25**	**0.62**	**0.31**
Mortality[a,b]	98.41±0.02	81.36±2.24	100 ± 0	100 ± 0	20.20 ± 3.79	3.33 ± 3.33

[a] Corrected according to Scheider-Orelli's formula. Values are means of three replicates. [b] Doses needed to give 50 and 90% mortality: LC_{50}: 1.49 (1.13-1.86) and LC_{90}: 4.80 (4.09-5.88). Values in parenthesis indicate 95% confidence limits: lower, upper.

CONCLUSION

In conclusion, an I_2/DMSO-mediated biomimetic protocol for the synthesis of furan rings from α-isopropylidene ketones was developed. The utility of the method was demonstrated by the synthesis of different bioactive furan terpenes **2-4** and specially the guaiazulene linderazulene (**5**), which was revealed to be a potent garrapaticide. Furthermore, in some cases, the corresponding bioactive dienelactone derivatives can also be generated in moderate yields in this transformation.

EXPERIMENTAL SECTION

General Remarks.

Silica gel SDS 60 (35-70 µm) was used for flash column chromatography. NMR spectra were acquired with Varian Direct-Drive 600 (^{1}H 600 MHz/^{13}C 150 MHz), Varian Direct-Drive 500 (^{1}H 500 MHz/^{13}C 125 MHz), Varian Direct-Drive 400 (^{1}H 400 MHz/^{13}C 100 MHz) and Varian Inova Unity 300 (^{1}H 300 MHz/^{13}C 75 MHz) spectrometers. Accurate mass determinations were achieved with a SYNAPT G2-Si Quadrupole-time-of-flight mass spectrometer (Waters, Milford, MA, USA) equipped with high-efficiency T-Wave ion mobility and an orthogonal Z–spray™ electrospray ionization (ESI) source was used for mass analyses. MassLynx v.4.1 software was used for HRMS instrument control, peak detection, and integration. The reactions were monitored by TLC, which were performed on 0.25-mm E. Merck silica gel plates (60F-254) and involves the use of UV light for visualization and solutions of phosphomolybdic acid in EtOH and heat as the developing agents. HPLC with UV light and RI

detection was also used. Semipreparative HPLC separations were conducted on a silica column (5 μm, 10 x 250 mm) at a flow rate of 2.0 mL/min using an Agilent Series 1100 instrument. The reagents were purchased at the highest quality that was commercially available and were used without further purification.

General procedure for the I_2/DMSO-mediated generation of furan rings from α-isopropylidene ketones

To a solution of the corresponding starting material (1 mmol) in the organic solvent (0.1 M) heated under reflux was added iodine (0.2-3 mmol) and DMSO (5 mmol). The solution was stirred at reflux and monitored by thin-layer chromatography analysis. Upon consumption of the starting material the reaction was diluted in *tert*-butyl methyl ether (MTBE) (100 mL), washed with a saturated solution of sodium thiosulfate (1 x 100 mL), and brine (1 x 100 mL). The organic layer was dried over sodium sulfate and evaporated *in vacuo*. Purification was performed by silica gel chromatography to yield chromatographically and spectroscopically pure product.

Reaction of pulegone (6) with the system I_2/DMSO: Synthesis of menthofuran (1).

The standard procedure was followed using 1 mmol (152 mg) of **6**, 0.2 mmol (51 mg) of iodine and DMSO as solvent, the reaction was heated at 60 ºC with a reaction time of 6.5 h. The crude product was purified by column chromatography over silica gel using mixture de hexanes (H) as eluent to obtain menthofuran (**1**) (112 mg, 75%)

*Menthofuran (**1**)*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (bs, 1H), 2.69 (dd, *J* = 16.0, 5.3 Hz, 1H), 2.46-2.31 (m, 2H), 2.20 (dd, *J* = 16.0, 9.5 Hz, 1H), 2.00-1.90 (m, 1H), 1.96 (d, *J* = 1.0 Hz, 3H), 1.91-1.83 (m, 1H), 1.39 (dddd, *J* = 13.2, 10.9, 10.1, 5.8 Hz, 1H), 1.12 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.7, 136.8, 119.6, 117.4, 31.5, 31.4, 29.6, 21.5, 19.9, 8.1. The spectroscopic data found for this compound matched those reported in the literature.[9a]

Reaction of pulegone (6) with the system I_2/DMSO: Synthesis of mintlactone (7) and compounds 8 and 10.

The standard procedure was followed using 1 mmol (152 mg) of **6**, 1 mmol (254 mg) of iodine, MTBE as solvent heated at a reflux temperature and with a reaction time of 25 h. The crude product

was purified by column chromatography over silica gel using mixtures of H and MTBE of increasing polarity as eluent to obtain 57 mg (35%) of compound **7** (H/MTBE 4:1), 29 mg (18%) of compound **8** (H/MTBE 4:1) and 25 mg (14%) of compound **10** (H/MTBE 2:1).

*(R)-3,6-Dimethyl-5,6-dihydrobenzofuran-2(4H)-one (**7**)*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, *J* = 3.3 Hz, 1H), 2.74 (dt, *J* = 17.1, 5.0 Hz, 1H), 2.63–2.55 (m, 1H), 2.48 (dddq, *J* = 17.6, 11.1, 4.8, 1.6 Hz, 1H), 1.98 (dq, *J* = 13.3, 4.9 Hz, 1H), 1.87 (bs, 3H), 1.46 (dddd, *J* = 13.4, 11.3, 8.9, 4.7 Hz, 1H), 1.15 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.5, 149.1, 148,1, 119.7, 114.0, 30.9, 29.7, 21.6, 21.1, 8.3. The spectroscopic data found for this compound were identical to those reported in the literature.[26]

*(R)-3,6-dimethyl-5,6-dihydrobenzofuran-7(4H)-one (**8**)*. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (q, *J* = 1.2 Hz, 1H), 2.73–2.61 (m, 2H), 2.61–2.54 (m, 1H), 2.22 (dq, *J* = 13.7, 4.6 Hz, 1H), 2.00 (d, *J* = 1.0 Hz, 3H), 1.91 (dddd, *J* = 13.5, 10.6, 9.3, 5.5 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.1, 147.4, 144,5, 139.7, 120.6, 41.8, 32.2, 20.1, 14.9, 7.8. The ^{1}H NMR data found for this compound were identical to those reported in the literature.[18]

*(R,Z)-2-(4-Methyl-2-oxocyclohexylidene)propanoic acid (**10**)*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.66 (bd, *J* = 13.9 Hz, 1H), 2.40–2.31 (m, *J* = 11.4, 3.2 Hz, 2H), 2.04–1.92 (m, 2H), 1.78 (bs, 3H), 1.24 (t, *J* = 12.8 Hz, 1H), 1.00 (dq, J = 13.0, 4.2 Hz, 1H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 172.6, 160.7, 121.2, 103.7, 45.9, 35.0, 29.1, 24.4, 21.0, 8.1. The spectroscopic data found for this compound were identical to those reported in the literature.[27]

Reaction of pulegone (6) with NIS/ Toluene: Synthesis of compound 9.

The standard procedure was followed using 1 mmol (152 mg) of **6**, 0.2 mmol (45 mg) of NIS and toluene as solvent heated at 60º C with a reaction time of 0.2 h. The crude product was purified by column chromatography over silica gel using H as eluent to obtain a compound **9** (49 mg, 52%).

*2-Isopropyl-3,6-dimethylbenzofuran (**9**)*. Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.9 Hz, 1H), 7.22 (bs, 1H), 7.03 (bd, *J* = 7.9 Hz, 1H), 3.17 (hept, *J* = 7.0 Hz, 1H), 2.47 (s, 3H), 2.17 (s, 3H), 1.33 (d, *J* = 7.0 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.0, 154.2, 133.2, 128.3, 123.3, 118.3, 111.1, 107.4, 26.5, 21.7 21.3 (x 2C), 7.9. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}O$ 189.1279; Found 189.1277.

Reaction of elemenone (12) with the system I_2/DMSO: Synthesis of curzerene (2) and curzerenone (14)

The standard procedure was followed using 1 mmol (218 mg) of **12**, 0.2 mmol (51 mg) of iodine, DMSO as solvent (60 ºC) and with a reaction time of 5 h. The crude product was purified by column chromatography over silica gel using (H/MTBE 99:1) to obtain curzurene (**2**) (179 mg, 83%).

Curzerene (2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (bs, 1H), 5.91 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.02 (dd, *J* = 17.5, 0.9 Hz, 1H), 5.00 (dd, *J* = 10.8, 0.9 Hz, 1H), 4.90 (bs, 1H), 4.78 (bs, 1H), 2.70 (bd, *J* = 16.3 Hz, 1H), 2.47-2.43 (m, 2H), 2.39 (d, *J* = 16.3 Hz, 1H), 2.32 (t, *J* = 7.2 Hz, 1H), 1.95 (d, *J* = 1.3 Hz, 3H), 1.77 (s, 3H), 1.10 (s, 3H); ^{13}C{^{1}H} NMR(150 MHz, $CDCl_3$): δ 149.6, 147.2, 147.1, 137.2, 119.3, 116.5, 112.7, 111.0, 50.0, 40.1, 36.1, 24.5, 24.2, 19.5, 8.1. The spectroscopic data found for this compound were identical to those reported in the literature.[10b]

The standard procedure was followed using 1 mmol (218 mg) of **12**, 1 mmol (254 mg) of iodine, toluene as solvent and with a reaction time of 30 min. The crude product was purified by column chromatography over silica gel using gel using H and MTBE of increasing polarity as eluent to obtain 16 mg (7%) of compound **13** (H/MTBE 99:1), 43 mg (20 %) of curzurene (**2**) (H/MTBE 99:1), and 48 mg (21%) of curzerenone (**14**) (H/MTBE 9:1).

9-Ketocurzerene (13). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (q, *J* = 1.1 Hz, 1H), 5.93 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.16 (dd, *J* = 10.7, 0.7 Hz, 1H), 5.10 (dd, *J* = 17.5, 0.6 Hz, 1H), 4.85 (q, *J* = 1.6 Hz, 1H), 4.77 (sa, 1H), 2.95 (dd, *J* = 17.1, 5.6 Hz, 1H), 2.88 (t, *J* = 5.1 Hz, 1H), 2.64 (dd, *J* = 17.1, 4.7 Hz, 1H), 2.00 (d, *J* = 1.2 Hz, 3H), 1.57 (dd, *J* = 1.5, 0.7 Hz, 3H), 1.26 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 188.4, 146.9, 145.5, 144.8, 141.1, 137.3, 120.6, 115,1, 114.6, 53.7, 52.3, 24.4, 23.2, 18.3, 7.7. The spectroscopic data found for this compound were consistent with to those reported in the literature.[21]

Curzurenone (14). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.48 (s, 1H), 5.16 (dd, *J* = 10.7, 0.7 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 5.02 (d, *J* = 17.4 Hz, 1H), 4.93 (q, *J* = 1.6 Hz, 1H), 4.79 (sa, 1H), 2.75 (ddd, *J* = 17.3, 5.2, 1.3 Hz, 1H), 2.64 (ddd, *J* = 17.3, 8.5, 1.1 Hz, 1H), 2.48 (dd, *J* = 8.5, 5.1 Hz, 1H), 1.90 (bs, 3H), 1.71 (bs, 3H), 1.16 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 171.3, 148.8, 147.8, 145.8, 145.1, 120.4, 114,7, 114.4, 113.5, 50.7, 41.8, 25.4, 23.8, 22.0, 8.45. The spectroscopic data found for this compound matched those reported in the literature.[22]

Reaction of germacrone (11) with the system I_2/DMSO: Synthesis of atractylone (3) and its isomer 4.

The standard procedure was followed using 1 mmol (218 mg) of **11**, 1 mmol (254 mg) of iodine, and hexane as solvent (room temperature) with a reaction time of 48 h. The crude product was purified by column chromatography over silica gel using (H/MTBE 95:5) to obtain 252 mg (74%) of a 5:1 mixture of the iododerivatives **20** and **21**. This mixture was subjected to HPLC (normal phase, H), to give pure **20** (Rt = 18.5 min) and pure **21** (Rt = 23.2 min).

*(4aS,8R,8aR)-8-Iodo-3,8a-dimethyl-5-methylene-4,4a,5,6,7,8,8a,9-octahydronaphtho[2,3-b]furan **20.*** Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (bs, 1H), 4.92 (q, J = 1.7 Hz, 1zH), 4.82 (bs, 1H), 4.46 (dd, *J* = 12.5, 4.1 Hz, 1H), 2.76 (d, *J* = 15.4 Hz, 1H), 2.50-2.15 (m, 7H), 1.96 (d, *J* = 1.2 Hz, 3H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.0, 146.6, 137.4, 119.2, 115.9, 109.5, 50.3, 45.4, 41.8, 41.4, 39.4, 37.6, 22.4, 15.1, 8.2. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}OI$ 343.0559; Found 343.0543.

*(4aS,8R,8aR)-8-Iodo-3,5,8a-trimethyl-4,4a,7,8,8a,9-hexahydronaphtho[2,3-b]furan **21.*** Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (bs, 1H), 5.21 (s, 1H), 4.50 (dd, *J* = 11.6, 5.7 Hz, 1H), 2.91–2.80 (m, 1H), 2.77–2.65 (m, 3H), 2.40 (d, *J* = 12.4 Hz, 1H), 2.32 (d, *J* = 16.1 Hz, 1H), 2.07 (dddd, *J* = 15.4, 12.0, 3.1, 1.5 Hz, 3H), 1.96 (d, *J* = 1.1 Hz, 3H), 1.96 (bs, 3H), 0.94 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.2, 137.9, 134.9, 122.3, 119.2, 116.7, 47.0, 44.3, 41.6, 38.6, 38.0, 22.8, 21.0, 13.3, 8.2. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}OI$ 343.0559; Found 343.0538.

*Reduction of **20** and **21** with nBu_3SnH/AIBN*. To a solution of *n*Bu_3SnH (0.30 mL, 1.16 mmol) and AIBN (10 mg, 0.06 mmol) in dry and deoxygenated bencene (4.5 mL), was added dropwise at 90ºC and under an argon atmosphere, a solution of compound **20** (100 mg, 0.29 mmol) in 1.5 mL of benzene for 15 min. When the addition was completed, the reaction mixture was let to react for additional 50 minutes, and then, the solvent was evaporated *in vacuo*. The mixture was diluted with MTBE (10 mL) and then washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (H:MTBE, 97:3) provided 34 mg (54%) of atractylon (**3**).

*Atractylon (**3**)*. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (bs, 1H), 4.89 (s, 1H), 4.73 (s, 1H), 2.48–2.28 (m, 5H), 2.17–2.11 (m, 1H), 2.08 (bt, *J* = 13.3 Hz, 1H), 1.98 (s, 3H), 1.76–1.48 (m, 4H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 149.9, 149.4, 136.9, 119.6, 116.2, 107.3, 45.8, 41.9, 39.3, 37.3,

36.7, 23.6, 20.9, 17.6, 8.2 The spectroscopic data for this compound matched with those reported in the literature.[10a]

When the same process was performed with compound **21**, a 56% of compound **4** was obtained.

*Isoatractylon (**4**).* ^{1}H NMR (500 MHz, CD_3COCD_3) δ 7.13 (bs, 1H), 5.44 (bs, 1H), 2.65 (dd, *J* = 15.5, 4.2 Hz, 1H), 2.65 (dd, *J* = 15.5, 4.2 Hz, 1H), 2.37 (bd, *J* = 17.4 Hz, 1H), 2.32 (dd, *J* = 15.7, 1.0 Hz, 1H),2,21-2,11(m,2H), 2.03-1.95 (m, 2H), 1.94 (bs, 3H), 1.73 (s, 3H), 1.62-1.50 (m, 2H), 0.83 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, CD_3COCD_3): δ 149.8, 137.1, 134.3, 121.6, 119.3, 117.0, 43.7, 38.4, 36.8, 32.9, 22.5, 21.0, 20.6, 15.9, 7.2. The spectroscopic data found for this compound were consistent with to those reported in the literature.[7]

Reaction of eudesmanes 16 and 17 with the system I_2/DMSO: Synthesis of atractylone (3) and isoatractylone (4).

The standard procedure was followed in both cases using 0.5 mmol (107 mg) of **16** or **17**, 0.1 mmol (25 mg) of iodine, MTBE as solvent and with a reaction time of 6 h. The crude product was purified by column chromatography over silica gel using (H/MTBE 97:3) to obtain atractylone (**3**) (86 mg, 80%) from **16**, and of isoatractylone (**4**) (89 mg, 82%) from 17.

Reaction of 4,5-epoxygermacrone (22) with the system I_2/DMSO: Synthesis of 23-26 and linderazulene (5)

The standard procedure was followed using 1 mmol (234 mg) of **22**, 0.4 mmol (102 mg) of iodine using MTBE as solvent and with a reaction time of 1 h 30 min. The crude product was purified by column chromatography over silica gel using mixtures of H and MTBE of increasing polarity as eluent to obtain 4 mg (2%) of linderazulene (H), 49 mg (21%) of compound **23** (H/MTBE 2:1), 75 mg (32%) of a 1:1 mixture of compounds **24** and **25** (H/MTBE 2:1), and 7 mg (3%) of compound **26** (H/MTBE 1:1).

*Linderazulene (**5**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.46 (d, J = 3.4 Hz, 1H), 7.44 (d, J = 1.5 Hz, 1H), 7.31 (s, 1H), 7.27 (d, J = 3.8 Hz, 1H), 2.85 (s, 3H), 2.75 (s, 3H), 2.40 (d, J = 1.3 Hz, 3H).; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.55, 139.38, 139.02, 135.62, 133.11, 131.41, 126.95, 125.15, 121.12, 119.54, 115.91, 111.23, 24.51, 13.09, 8.09. The spectroscopic data found for this compound were consistent with those reported in the literature.[8a]

(1R,8aR)-1-Hydroxy-1,4-dimethyl-7-(propan-2-ylidene)-2,7,8,8a-tetrahydroazulen-6(1H)-one (***26***). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (q, *J* = 2.7 Hz, 1H), 5.95 (s, 1H), 2.77-2.69 (m, 2H), 2.55 (bd, *J* = 17.5 Hz, 1H), 2.48 (dd, *J* = 17.5, 3.4 Hz, 1H), 2.03 (d, *J* = 1.2 Hz, 3H), 1.98 (bt, *J* = 13.3 Hz, 1H), 1.88 (s, 3H), 1.81 (s, 3H), 1.24 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 196.1, 144.0, 142.0, 139.9, 134.8, 132.7, 130.3, 82.5, 57.8, 47.1, 26.7, 22.9, 22.7 (x 2C), 21.3. HRMS (ESI-QTOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}O_2$ 233.1542 $[M+H]^+$; Found 233.1535.

Reaction of 23-26 with the system I_2/DMSO: Synthesis of linderazulene (5)

The standard procedure was followed using 120 mg of **23-26**, 0.25 mmol (64 mg) of iodine using toluene as solvent and with a reaction time of 5 min. The crude product was purified by flash column chromatography (H) to obtain linderazulene (**5**) (49 mg, 46%).

Reaction of 4,5-epoxygermacrone (22) with the system I_2/DMSO: Synthesis of linderazulene (5)

The standard procedure was followed using 1 mmol (234 mg) of **22**, 0.5 mmol (127 mg) of iodine and 30 mmol (2.13 mL) of DMSO using toluene as solvent and with a reaction time of 5 min. The crude product was purified by flash column chromatography (H) to obtain a linderazulene (**5**) (44 mg, 21%).

Insect bioassays

Spodoptera littoralis, *Myzus persicae* and *Rhopalosiphum padi* colonies were reared on artificial diet, bell pepper (*Capsicum annuum*) and barley (*Hordeum vulgare*) plants respectively, and maintained at 22 ± 1 ºC, >70% relative humidity with a photoperiod of 16:8 h (L:D) in a growth chamber.

The bioassays were conducted with ten-twenty newly emerged *S. littoralis* L6 larvae and two hundred *M. persicae* or *R. padi* adults. Feeding or settling inhibition (% FI or % SI) were calculated as reported[17] and the antifeedant effects (FI/SI) were analyzed for significance by the non-parametric Wilcoxon signed-rank test.

Ixodicidal bioassay.

Engorged females of the tick *Hyalomma lusitanicum* Koch 1844 (Ixodoidea: Ixodida) were collected from their host (deer) in central Spain (Finca La Garganta. Ciudad Real), and maintained at 22-24ºC. 70% RH until oviposition and larval hatching. Larvae (4-6 weeks old) were used for the bioassay as described by Ruiz-Vásquez *et al*.[28] The larvicidal activity data are presented as percentage of mortality corrected according to Schneider-Orelli's formula.[29] Lethal doses (LC_{50} and LC_{90}) were calculated by Probit Analysis (five 1:2 serial dilutions. STATGRAPHICS Centurion XVI. version 16.1.02).

ASSOCIATED CONTENT

Supporting Information.

This material is available free of charge via on the ACS Publications website at DOI:

Copies of ^{1}H and ^{13}C NMR spectra, and mechanistic proposal for the formation of compounds **7**, **8** and **10** (PDF).

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Notes

The authors declare no competing financial interest.

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