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# Regioselective Ene-Type Allylic Chlorination of Electron Rich Alkenes by Activated DMSO

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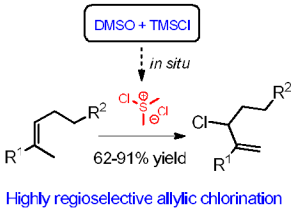
[a] Department of Chemistry; Aristotle University of Thessaloniki, Main University Campus, Laboratory of Organic Chemistry, 54124, Thessaloniki, Greece; Corresponding author E-mail: alzograf@chem.auth.gr




**Abstract:**

A simple protocol involving the activation of DMSO by chlorotrimethysilane is described for the chemoselective chlorination of polyprenoids. The proposed protocol provides a versatile, scalable and alternative to existing routes method for accessing useful synthetic synthons for the synthesis of complex terpenoids.

Halogenated and epoxidized acyclic polyprenoids are regarded as useful synthetic intermediates for the synthesis of cyclized terpenoids following their well established biomimetic cationic cyclizations[1] or the less developed production of organometallic nucleophiles.[2] Although, several methods exist for their regio- and stereoselective epoxidation, methods describing their allylic halogenation still face serious regioselectivity issues mainly due to the similar electronics possessed by the alkenes of the applied polyunsaturated substrates. Among the most reliable methods for the ene-type halogenation are: the chlorination by chlorine gas in apolar solvents,[3] the use of sulfynyl chloride[4] and the halosuccinimide reagents in combination with metals (Figure 1).[5] On the other hand, halogenation methods which are based on the prefunctionalization of the targeted alkenes by epoxidations and dihydroxylations require additional steps but also they usually fail to provide clean, quantitative transformations.[5]

Activation of DMSO is a well known process which is used in a wide range of useful transformations,[6] such as the oxidation of alcohols or their chlorination,[7] and the formation of C-C bonds through the various versions of the Pummerer-type reactions (Figure 1).[8] On the other hand, activated sulfoxides are rather underused in the preparation of halogenated products in a regioselective fashion. To the best of our knowledge, only some scarce examples exist in the literature which describe their ability to mono- or dihalogenate styrenes,[9] enamines[10] or stabilized enols,[11] usually as part of observed byproducts from Swern-type oxidations.

It is known that DMSO and TMSCl provide a reliable *in situ* protocol for the production of methanesulfenyl chloride (**1**).[12] Applications of this powerful reagent have been well documented[13] in its ability to act as a mild electrophile for the direct chlorination of alcohols,[7] the regioselective opening of epoxides,[14] but most importantly the *anti*-chlorosulfenylation of alkenes.[13] The latter reaction is described to involve a chloride based thiranium cation opening, to provide *anti*-Markovnikov addition of chloro and methylthio groups to the alkene (Figure 1).[15] Based on this mechanism, we anticipated that the stabilization of dimethylsulfide cation intermediate (**2**) would allow us to get a convenient access to ene-type chlorinated products of electron rich alkenes (Figure 1).

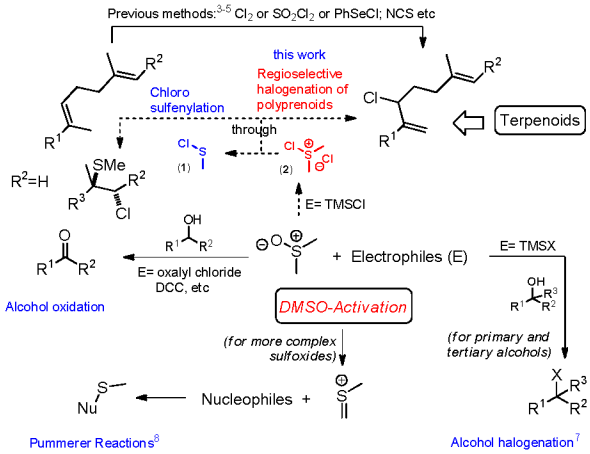


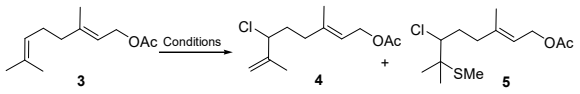

**Figure 1.** The most utilized applications of activated DMSO and the proposed expansion in the ene-type halogenation of polyprenoids.

Despite the previous efforts to establish a general chlorination method for styrenes by utilizing activated DMSO that led to rather unpredictable mixtures of mono- and dichlorinated products,[9] ene-type allylic halogenation of alkenes with stable hydrohalide salts of DMSO ,[16] supports the feasibility of our idea. Forced by our constant interest in the synthesis of complex sesquiterpenoids,[17] we sought to develop a versatile, scalable protocol for the regioselective formation of allylic chlorides of polyprenoids under mild reaction conditions.

Rationalizing the idea above (Figure 1), we started by investigating the feasibility of interrupting the chlorosulfenylation process, in the known DMSO-TMSCl protocol, to selectively produce allylic chlorides. Geraniol acetate (**3**), bearing two electronically different alkenes was chosen as a simple model for this study (Table 1). Our first attempt, utilizing the exact previously reported chlorosulfenylation conditions, failed to provide the desired product **4**, producing only compound **5**, albeit in low yield (entry 1; Table 1). As expected, allowing the substrate to react at higher temperature (60 $^{o}$C) led only to decomposition (entry 2; Table 1). On the other hand, a clear indication for the interruption of this process came from the utilization of higher excess of chlorotrimethylsilane (6 equiv) at ambient temperature, providing the desired compound **4**, as the minor component, along with the thiochlorinated derivative **5**, as an inseparable mixture of products (entry 3; Table 1). Further experimentation, utilizing DMSO in DCM or nitromethane as solvents allowed the chemoselective production of the desired chloride **4**, in moderate yields, but still without avoiding the chlorosulfenylated product **5** (entries 4-5; Table 1).

Gratifyingly, a great improvement was made when a 5 min premixing time period of chlorotrimethylsilane and DMSO was allowed before the introduction of the substrate. In these cases, cleaner reaction profiles were evidenced by $^{1}$H-NMR indicating the absence of chlorosulfenylated products. Longer premixing times led to unidentified products and low conversion rates of the substrate. Thus, the premixing time was kept to a strict 5 min window in all further attempts (entries 6-10; Table 1). Polarity screening, under these premixing conditions, led to the identification of DCM as the optimal solvent. Excess of trimethylsilane compared to DMSO, at lower temperatures, was advantageous not only for the higher conversion rates of the substrate but also for the minimization of the byproduct **5** (entries 6-7; Table 1). In general, high excess of DMSO (up to 5 equiv) usually does not affect the regioselective monochlorination of the product leading to faster reactions. However, harsher reaction conditions, as described by the presence of more equiv of DMSO and/or the addition of LiCl in the reaction mixture, force the reaction to also chlorinate the next more electron rich alkene, though usually in low yields (approx. 25-30%).

**Table 1**. Reaction Optimization[a]

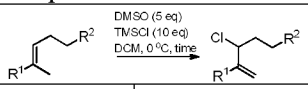


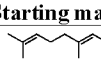
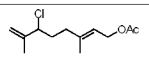
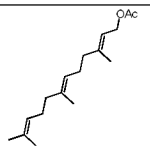
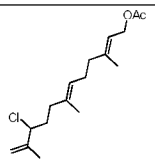
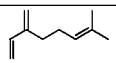
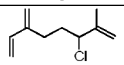
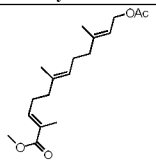
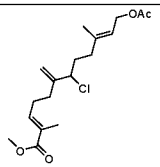
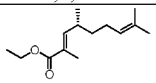
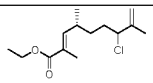
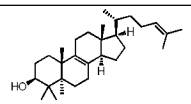
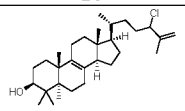
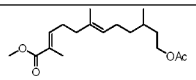
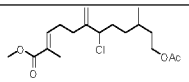

| Entry | Solvent | Condi-tions[a] | equiv TMSCl | equiv DMSO | Conve-rsion of **3** (%) | Yield (%)[b] **4**; **5** |
|---|---|---|---|---|---|---|
| 1[c] | DMSO | 48h, rt | 1.5 | excess | 38 | 0; 23 |
| 2[c] | DMSO | 5h, 60 $^{o}$C | 1.5 | excess | 100 | Decomp. |
| 3[c] | DMSO | 3.5h, rt | 6.0 | excess | 90 | 22; 37 |
| 4[c] | DCM | 48h, rt | 1.5 | 3.0 | 84 | 52; 25 |
| 5[c] | MeNO2 | 5h, rt | 1.5 | 3.0 | 100 | 41; 45 |
| 6 | DCM | 24h, rt | 1.5 | 1.5 | 70 | 55; traces |
| 7 | DCM | 5h, 0 $^{o}$C | 5.0 | 2.5 | 100 | 91; 0 |
| **8** | **DCM** | **2h, 0 $^{o}$C** | **10** | **5** | **100** | **92; 0** |
| 9 | toluene | 12h, 0 $^{o}$C | 10 | 5 | 30 | Unknown |
| 10 | THF | 12h, 0 $^{o}$C | 10 | 5 | 100 | Unknown |
| 11 | CH3CN | 12h, 0 $^{o}$C | 10 | 5 | 75 | 50, 30 |
| 12 | AcOEt | 12h, 0 $^{o}$C | 10 | 5 | 80 | 40, 40 |

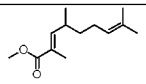
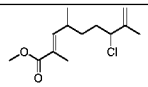
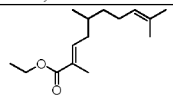
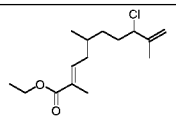
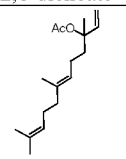
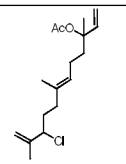
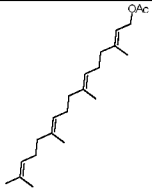
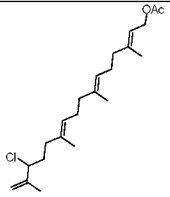
[a] All reactions were carried out as followed unless otherwise noted: In 4.0 mL screw capped vials are introduced DMSO and TMSCl in the indicated solvent. The mixture is stirred for 5 min in the indicated temperature before a solution of the substrate was introduced and stirred for the provided time and temperature. [b] The yields are established by $^1$H NMR using internal standard. [c] No premixing time of DMSO and TMSCl was used.

With these optimal conditions in hand, next, we sought to find the scope of the reaction in more challenging substrates, bearing either multiple electronically similar alkenes and/or different substituents. According to Table 2, in polyprenoids like farnesol acetate, the saturated to the allylic acetate congener or even geranylgeranyl acetate, the reaction works smoothly to provide good to high yields of monochlorinated products **6**, **12** and **16** respectively. Interestingly, although these substrates can further react, if purified and resubjected to the same reaction conditions, this does not affect the reproducibility of the parent reaction in providing the monochlorinated product
Sensitive to polymerization triene compounds like myrcene, react only on the trisubstituted alkene side to give compound **7** in almost quantitative yield.

**Table 2**. Substrate Scope[a]




| Entry | Starting material | Product | Yield |
|---|---|---|---|
| 1 |  geranyl acetate |  **4** | 91%[b] in 5h<br>79%[c] in 5h |
| 2 |  farnesyl acetate |  **6** | 87% in 3h |
| 3 |  myrcene |  **7** | 91% in 1.5h<br>74%[c] in 1.5h |
| 4 |  (10E) Z-methyl 12-acetoxy-2,6,10-trimethyl-dodeca-2,6,10-trienoate |  **8** | 68% in 12h |
| 5 |  E-ethyl 2,4,8-trimethylnona-2,7-dienoate |  **9** | 82% in 4.5h |
| 6 |  2,3-dimethyl-2-butene |  **10** | 42% in 2h |
| 7 |  lanosterol |  **11** | 78% in 3h |
| 8 |  6-methyl 12-acetoxy-2,6,10-trimethyldodeca-2,6-dienoate |  **12** | 62% in 12h |

| | | | |
|---|---|---|---|
| 9 |  E-methyl 2,4,8-trimethylnona-2,7-dienoate |  **13** | 87%[b] in 2h |
| 10 |  E-ethyl 2,5,9-trimethyldeca-2,8-dienoate |  **14** | 69%[b] in 5.5h |
| 11 |  (E)-3,7,11-trimethyldodeca-1,6,10-trien-3-yl-acetate |  **15** | 75%[b] in 4h |
| 12 |  geranylgeranyl acetate |  **16** | 81%,in 2.5h |

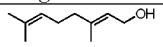
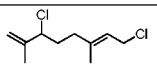
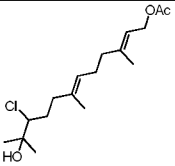
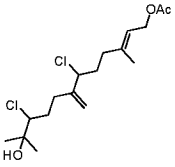
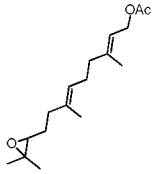
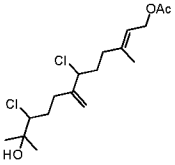
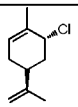
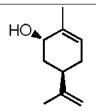
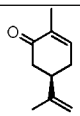
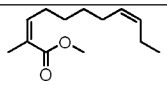
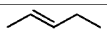
[a] All reactions were carried out in screw capped 4 mL vials. DMSO and TMSCl both in DCM were mixed for 5 min at 0 $^{o}$C before the introduction of the solution of the substrate (0.1 M; 0.1 mmoles) in DCM; [b] 2.5 equiv of DMSO and 5 equiv of TMSCl were used instead of the regular conditions; [c] yields for 2 mmoles scale for the substrate under the regular conditions.

Due to reaction's base free nature, substituents as esters but also halogens and allylic chiral centers are well tolerated (compounds **9**, **13** and **11**; Table 2 and **18**; Table 3) providing good yields of chlorinated products. On the other hand, sensitive to acid groups and groups that can also react with activated DMSO, like primary and tertiary alcohols,[9] but also epoxides, are cleanly transformed into chlorides and chlorohydrins respectively, a result that supports previous reports on chlorosulfenyl chemistry.[9] Thus, when substrates bearing epoxides and alcohols are used, it is feasible to directly produce the polychlorinated products (Entries 1-3, Table 3).

Different reaction outcomes were resulted when α-pinene and *trans*-carveol were used as substrates (Entry 4 and 5, Table 3). In these cases chlorinated compounds were delivered either by cyclobutane ring opening (compound **19**; entry **4)** or by SN2 and SN2′ substitution of the allylic alcohol (diastereoisomeric compounds compounds **19** and **20**; entry 5). Interestingly, α-pinene reaction was not attributed to the presence of hydrochloric acid but rather to the direct activation of cyclobutane core by activated DMSO.[18]

Finally, utilization of *cis*- or *trans*-disubstituted alkenes as substrates (Entries 6, 7, 8; Table 3), failed to provide any product, even after prolonged reaction times under harsh conditions.

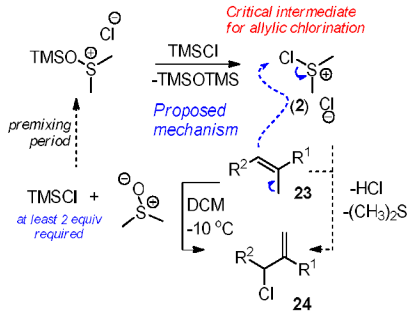
**Table 3**. Reaction of DMSO/TMSCl with different functional groups[a]

| Entry | Starting material | Product | Yield |
|---|---|---|---|
| 1 |  geraniol |  **17** | 78%, in 3h |
| 2 |  (2E,6E)-10-chloro-11-hydroxy-3,7,11-trimethyldodeca-2,6-dien-1-yl acetate |  **18** | 42%, in 12h |
| 3 |  (2E,6E)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-yl acetate |  **18** | 25%, in 3h or 43% in 12h |
| 4 |  a-pinene |  **19** | 82%, in 12h |
| 5 |  trans-carveol | **19** and  **20** | 88% in 3h as an inseparable mixture of **19**:**20** in 1:1 ratio |
| 6 |  S-carvone | No reaction | - |
| 7 |  (2Z,8Z)-methyl 2-methylundeca-2,8-dienoate | No reaction | - |
| 8 |  trans-2-pentene | No reaction | - |

[a] All reactions were carried out in screw capped 4mL vials. DMSO (5 equiv) and TMSCl (10 equiv) both in DCM were mixed for 5min at 0°C before the introduction of a solution (0.1M) the substrate (0.1 mmoles).

This latter behavior greatly distinguishes our method from some of the previous reported which react with these substrates, allowing the utilization of our protocol in otherwise non-accessible products.

The reaction is proposed to involve the production of cation **2**, an established precursor for the *in situ* production of chlorosulfenyl chloride (Scheme 1). Attack of **2** by the alkene, followed by loss of a proton leads to the formation of the allylic chloride releasing hydrochloric acid and dimethylsulfide. Experimental evidence of dimethylsulfide and TMS-OTMS production corroborates to the suggested mechanism.




**Scheme 1**. Ene-type chlorination of polyprenoids: the proposed reaction mechanism.

In conclusion, we have developed an optimized protocol for the regioselective ene-chlorination of electron rich alkenes. This method enables the production of useful synthetic intermediates for the synthesis of terpenoids in moderate to high yields.

## Experimental Section

### General Experimental Methods.

All reactions were carried out in air unless otherwise noticed. Dry dichloromethane ($CH_2Cl_2$) is used in all reactions following the general procedure. Dichloromethane was dried by distillation from $CaH_2$ and directly used in the reactions. Anhydrous DMSO was purchased by Aldrich and kept under argon every time that is opened. Chlorotrimethylsilane was carefully dried with molecular sieves 4A and distilled under argon. The bottle was kept under argon every time that is opened in order to avoid its hydrolysis. Reagents were purchased at the highest commercial quality and used without further purification.
Reactions were monitored by thin-layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and ethanolic *p*-anisaldehyde as developing agent. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254).
NMR spectra were recorded on Agilent 500 spectrometer and calibrated using residual solvent peak. The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, brd = broad doublet, brt = broad triplet, pst = pseudo triplet. Microanalyses were performed on a Perkin-Elmer 2400-II element analyzer.

**Gerenal Experimental Procedure for the synthesis of allylic chlorides**:
In a dry round bottom flask, 2mL DCM, DMSO (1.0 mmole; 5 equiv) and TMSCl (2.0 mmoles; 10 equiv) are introduced sequentially at 0 °C. The mixture is stirred at 0 °C for 5 min before a solution of the alkene substrate (0.2 mmoles) in 2mL of DCM was added. The reaction is stirred at 0 °C for the indicated time for each reaction. After TLC shows consumption of the starting material the reaction is quenced by $NaHCO_3$ and extracted three times with DCM (3 x 6 mL). The organic layer is dryed with $Na_2SO_4$ filtered and evaporated to dryness. The oily residue was chromatographed with silica gel to provide the desired chlorinated product.

*(E)-6-chloro-3,7-dimethylocta-2,7-dien-1-yl acetate* (**4**).[19] Prepared according to the general experimental procedure starting from 39 mg (0.2 mmoles) of geranyl acetate in 5 h reaction time to provide compound **4** (42 mg, 91% yield). $R_f$ = 0.65 (hexanes/EtOAc = 3:1). $^1H$ and $^{13}C$ NMR are identical to the reported.[19]

*(2E, 6E)-10-chloro-3,7,11-trimethyldodeca-2,6,11-trien-1-yl acetate* (**6**).[5] Prepared according to the general experimental procedure starting from 53 mg (0.2 mmoles) of farnesyl acetate[20] in 3 h reaction

time to provide compound **6** (52 mg, 87% yield). $R_f$ = 0.77 (hexanes/EtOAc = 3:1). $^1$H and $^{13}$C NMR are identical to the reported.[5]

*3-chloro-2-methyl-6-methyleneocta-1,7-diene* (**7**).[21] Prepared according to the general experimental procedure starting from 27 mg (0.2 mmoles) of myrcene in 1.5h reaction time to provide compound **7** (31 mg, 91% yield). $R_f$ = 0.68 (hexanes/EtOAc = 3:1). $^1$H and $^{13}$C NMR are identical to the reported.[21]

*(2E,10E)-methyl 12-acetoxy-7-chloro-2,10-dimethyl-6-methylenedodeca-2,10-dienoate* (**8**). Prepared according to the general experimental procedure starting from 62 mg (0.2 mmoles) of (*2E,6E,10E*)-methyl 12-acetoxy-2,6,10-trimethyldodeca-2,6,10-trienoate[22] in 12 h reaction time to provide compound **8** (47 mg, 68% yield), as a clear oil.$R_f$ = 0.61 (hexanes/EtOAc = 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.75 (m, 1H), 5.37 (dt, 1H), 5.15 (s, 1H), 4.95 (d, 1H), 4.58 (d, 1H), 4.33 (m, 1H), 3.73 (s, 3H), 2.41-2.34 (m, 4H), 2.06 (s, 3H), 2.00-1.92 (m 1H), 1.70 (d, 3H); $^{13}$C NMR (125 MHz, CDCl3): δ = 171.1, 169.4, 147.2 (two carbons), 141.3, 140.4, 119.4, 113.3, 65.5, 61.2, 52.2, 36.5, 34.5, 29.3, 26.8, 16.5, 15.6, 12.5; Elemental Anal. Calcd for $C_{18}H_{27}ClO_4$: C, 63.06; H, 7.94; Cl, 10.34. Found: C, 63.21; H, 7.65; Cl, 10.38.

*(E)-ethyl 7-chloro-2,4,8-trimethylnona-2,8-dienoate* (**9**). Prepared according to the general experimental procedure starting from 45 mg (0.2 mmoles) of (*E*)-ethyl 2,4,8-trimethylnona-2,7-dienoate[23] in 4.5 h reaction time to provide compound **9** (42 mg, 82% yield) as a mixture of isomers. Further purification was accomplished by flash chromatography of the mixture of isomers to deliver the pure enantiomer in 35% yield, as a clear oil. $[a]_D^{25}$ = - 33.21 (*c* 0.4, $CHCl_3$). $R_f$ = 0.72 (hexanes/EtOAc = 4:1. $^1$H NMR (500 MHz, $CDCl_3$): δ =6.50 (d, *J* = 9.7Hz, 1H), 4.98 (s, 1H), 4.89 (s, 1H), 4.38-4.25 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.55-2.39 (m, 1H), 1.84 (s, 3H), 1.78 (s, 3H), 1.61-1.51 (m, 2H), 1.46-1.37 (m, 1H), 1.29 (t, *J* = 7.2Hz, 3H), 1.27-1.22 (m, 1H), 1.02 (d, *J* = 6.7Hz, 3H); $^{13}$C NMR (125 MHz, CDCl3): δ = 168.2, 146.7, 144.2, 127.0, 114.2, 66.7, 60.5, 34.4, 34.3, 32.8, 20.0, 16.8, 14.2, 12.6; Elemental Anal. Calcd for $C_{14}H_{23}ClO_2$: C, 64.98; H, 8.96; Cl, 13.70. Found: C, 65.22; H, 8.81; Cl, 13.61.

*3-chloro-2,3-dimethylbut-1-ene* (**10**).[24] Prepared according to the general experimental procedure starting from 420 mg (5.0 mmoles) of 2,3-dimethyl-2-butene in 2 h reaction time to provide compound **10** (249 mg, 42% yield). The compound is highly volatile, labile and polymerizes in column and upon standing. The compound is purified by micro-distillation. $^1$H is identical to the reported.[24]

*(3S,5R,10R,13R,14R,17R)-17-((2R)-5-chloro-6-methylhept-6-en-2-yl)-4,4,5,10,13-pentamethyl-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-ol* (**11**). Prepared according to the general experimental procedure starting from 85 mg (0.2 mmoles) of lanosterol in 3 h reaction time to provide compound **11** (72 mg, 78% yield) as a mixture of isomers. Off white solid, $R_f$ = 0.54 (hexanes/EtOAc = 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 5.00 (s, 1H), 4.88 (s, 1H), 4.39-4.28 (m, 1H), 3.55 (d, *J* = 5.1Hz, 1H), 3.22 (dt, *J* = 14.2, 7.2 Hz, 1H), 2.07-1.13 (m, 23H), 1.79 (d, *J = 6.4* Hz, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.91 (d, *J* = 6.1Hz, 3H), 0.87 (s, 3H), 0.81 (s, 3H), 0.69 (s, 3H); $^{13}$C NMR (125 MHz, CDCl3): δ =144.7, 144.3, 134.4, 134.3 (two peaks), 114.3, 113.9, 79.0, 78.9, 67.5, 67.4, 50.4, 50.2 (two peaks), 49.8, 44.5 (two peaks), 42.0, 41.9, 39.5, 38.9, 37.0, 36.5, 36.0, 35.6, 33.4 (three peaks), 33.3, 30.9 (two peaks), 30.8 (two peaks), 30.2, 30.1, 29.7, 29.1, 28.2 (two peaks), 28.1 (two peaks), 28.0, 27.9, 27.8, 26.5, 24.2 (two peaks), 24.1, 22.8, 22.5, 21.0 (two peaks), 19.1, 18.7, 18.6, 18.2, 17.0, 16.7, 15.7, 15.4; Elemental Anal. Calcd for $C_{30}H_{49}ClO$: C, 78.13; H, 10.71; Cl, 7.69. Found: C, 78.38; H, 10.90; Cl, 7.50.

*(E)-methyl 12-acetoxy-7-chloro-2,10-dimethyl-6-methylenedodec-2-enoate* (**12**). Prepared according to the general experimental procedure starting from 62 mg (0.2 mmoles) of (*2E,6E*)-methyl 12-acetoxy-2,6,10-trimethyldodeca-2,6-dienoate[25] in 12 h reaction time to provide compound **12** (43 mg, 62% yield) as a mixture of isomers. Clear oil, $R_f$ = 0.59 (hexanes/EtOAc = 3:1). $^1$H NMR (500 MHz,

$CDCl_3$): δ = 6.80-6.69 (m, 1H), 5.14 (d, *J* = 1.1 Hz, 1H), 4.94 (d, *J* = 1.9 Hz, 1H), 4.41-4.30 (m, 1H), 4.12-4.03 (m, 2H), 3.73 (s, 3H), 2.42-2.08 (m, 4H), 2.04 (s, 3H), 1.86 (s, 3H), 1.74-1.67 (m, 1H), 1.61-1.52 (m, 5H), 1.37-1.30 (m, 1H), 0.92 (dd, *J* = 6.6, 1.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 171.1, 171.0, 168.5, 168.4, 147.5, 147.3, 141.3 (two peaks), 128.1 (two peaks), 113.2, 113.1, 66.5, 66.4, 62.7 (two peaks), 51.8, 51.7, 35.4 (two peaks), 34.1 (two peaks), 34.0, 33.9, 29.6, 29.5, 29.3, 26.9 (three peaks), 21.0 (two peaks), 19.4, 19.3, 12.5; Elemental Anal. Calcd for $C_{18}H_{29}ClO_4$: C, 62.69; H, 8.48; Cl, 10.28. Found: C, 62.61; H, 8.20; Cl, 10.46.

*(E)-methyl 7-chloro-2,4,8-trimethylnona-2,8-dienoate* (**13**). Prepared according the general experimental procedure starting from 42 mg (0.2 mmoles) of (*E*)-methyl 2,4,8-trimethylnona-2,7-dienoate[23] in 2 h reaction time to provide compound **13** (42 mg, 87% yield) as a mixture of isomers. Further purification by flash chromatography (hexanes/EtOAc = 80:1) delivered one diastereomeric pair of the mixture in 40% yield. Clear oil, $R_f$ = 0.58 (PS / EA= 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.56-6.45 (m, 1H), 4.98 (s, 1H), 4.88 (d, *J* = 1.2 Hz, 1H), 4.32 (td, *J* = 7.2, 2.9 Hz, 1H), 3.73 (s, 3H), 2.56-2.45 (m, 1H), 1.84 (s, 3H), 1.77 (s, 3H), 1.75-1.27 (m, 4H), 1.01 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ = 168.7, 147.2, 144.2, 124.2, 114.3, 66.8, 51.8, 34.4, 34.0, 32.9, 20.0, 16.9, 12.6; Elemental Anal. Calcd for $C_{13}H_{21}ClO_2$: C, 63.79; H, 8.65; Cl, 14.48. Found: C, 63.71; H, 8.71; Cl, 14.45.

*(E)-ethyl 8-chloro-2,5,9-trimethyldeca-2,9-dienoate* (**14**). Prepared according the general experimental procedure starting from 48 mg (0.2 mmoles) of (*E*)-ethyl 2,5,9-trimethyldeca-2,8-dienoate[26] in 5.5 h reaction time to provide compound **14** (38 mg, 69% yield) as a mixture of isomers. Clear oil $R_f$ = 0.68 (hexanes/EtOAc = 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 6.79-6.71 (m, 1H), 5.00 (s, 1H), 4.88 (s, 1H), 4.39-4.30 (pt, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.22-2.13 (m, 1H), 2.08-2.00 (m, 1H), 1.95-1.85 (m, 1H), 1.82 (s, 3H), 1.79 (s, 3H), 1.68-1.63 (m, 1H), 1.52-1.42 (m, 1H), 1.36-1.31 (m, 1H), 1.29 (t, *J* = 7.1Hz, 3H), 1.14 (m, 1H), 0.92 (d, *J* = 7.3 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ = 168.2, 168.1, 144.4, 144.2, 140.6, 140.5, 128.6, 124.5, 114.3, 114.1, 67.0, 66.9, 60.4, 60.3, 35.8 (two peaks), 34.2, 34.1, 33.9, 33.8, 32.7, 32.6, 19.6 (two peaks), 16.9, 16.8, 14.3 (two peaks), 12.5 (two peaks); Elemental Anal. Calcd for $C_{15}H_{25}ClO_2$: C, 66.04; H, 9.24; Cl, 13.00. Found: C, 66.12; H, 9.01; Cl, 13.07.

*(E)-10-chloro-3,7,11-trimethyldodeca-1,6,11-trien-3-yl acetate* (**15**).[5] Prepared according the general experimental procedure starting from 26 mg (0.1 mmoles) of (*E*)-3,7,11-trimethyldodeca-1,6,10-trien-3-yl acetate in 4 h reaction time to provide compound **15** (22 mg, 75% yield). $R_f$ = 0.64 (hexanes/EtOAc = 3:1). Elemental Anal. Calcd for $C_{17}H_{27}ClO_2$: C, 68.32; H, 9.11; Cl, 11.86. Found: C, 68.38; H, 9.32; Cl, 11.55; $^1$H and $^{13}$C NMR are identical to the reported.[5]

*(2E,6E,10E)-14-chloro-3,7,11,15-tetramethylhexadeca-2,6,10,15-tetraen-1-yl acetate* (**16**).[5] Prepared according the general experimental procedure starting from 33 mg (0.1 mmoles) of geranylgeranyl acetate in 2.5 h reaction time to provide compound **16** (30 mg, 81% yield) $R_f$ = 0.62 (hexanes/EtOAc = 3:1). Elemental Anal. Calcd for $C_{22}H_{35}ClO_2$: C, 72.01; H, 9.61; Cl, 9.66. Found: C, 72.12; H, 9.50; Cl, 9.60; $^1$H and $^{13}$C NMR are consistent with the reported.[5]

*(E)-3,8-dichloro-2,6-dimethylocta-1,6-diene* (**17**).[4a] Prepared according the general experimental procedure starting from 60 mg (0.4 mmoles) of geraniol in 3 h reaction time to provide compound **17** (112 mg, 78% yield) $R_f$ = 0.58 (hexanes/EtOAc = 3:1). $^1$H and $^{13}$C NMR are identical to the reported.[4a]

*(E)-6,10-dichloro-11-hydroxy-3,11-dimethyl-7-methylenedodec-2-enyl acetate* (**18**). Prepared according the general experimental procedure starting from 63mg (0.2 mmoles) of (*2E,6E*)-10-chloro-11-hydroxy-3,7,11-trimethyldodeca-2,6-dienyl acetate[24] in 12 h reaction time to provide compound **18** (30mg, 42%

yield) or alternatively prepared according to the general experimental procedure starting from 56 mg (0.2 mmoles) of (*2E,6E*)-9-(3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dienyl acetate.[24] The mixture is stirred for 2 h at 0 °C before readditing a premixed mixture of DMSO (5 equiv) and TMSCl (10 equiv) in DCM. The mixture is stirred for an additional 10 h at the same temperature to provide compound **20** as a mixture of isomers (30 mg, 43% yield). Clear oil, $R_f$ = 0.51 (hexanes/EtOAc = 3:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 5.37 (t, *J* = 7.0 Hz, 1H), 5.16 (s, 1H), 4.97 (s, 1H), 4.58 (d, *J* = 7.0 Hz, 2H), 4.34 (td, *J* = 8.1, 4.8 Hz, 1H), 3.91-3.82 (m, 1H), 2.65-2.55 (m, 1H), 2.24-1.92 (m, 6H), 2.05 (s, 3H), 1.85-1.72 (m, 2H), 1.71 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ = 171.1 (two peaks), 147.3, 147.0, 140.35 (two peaks), 119.6, 119.4, 113.8, 113.4, 73.1, 72.8, 65.5, 65.1, 61.3, 61.2, 61.1, 61.0, 36.5 (two peaks), 34.6, 34.4, 31.4, 31.3, 28.8, 28.7, 26.4 (two peaks), 25.5, 25.4, 21.1, 21.0, 16.5, 16.4; Elemental Anal. Calcd for $C_{17}H_{28}Cl_2O_3$: C, 58.12; H, 8.03; Cl, 20.18. Found: C, 58.41; H, 7.86; Cl, 20.31.

*trans-(+)-6-chloro-p-mentha-1,8-diene* (**19**).[27] Prepared according the general experimental procedure starting from 27 mg (0.2 mmoles) of a-pinene in 12 h reaction time to provide compound **19** (28 mg, 82% yield). $R_f$ = 0.49 (hexanes/EtOAc = 3:1). $^1$H and $^{13}$C NMR and optical rotation are identical to the reported.[28]

*trans-6-chloro-p-mentha-1,8-diene* (**19**) and *cis-6-chloro-p-mentha-1,8-diene* (**20**).[27] Prepared according the general experimental procedure starting from 30 mg (0.2 mmoles) of *trans*-carveol in 3.5 h reaction time to provide an inseparable mixture of compounds **19** and **20** (30 mg, 88% yield). $R_f$ = 0.8 (hexanes/EtOAc = 5:1). $^1$H and $^{13}$C NMR are identical to the reported.[28]

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**Supporting Information**
Indicative copies of $^1$H and $^{13}$C NMR spectra of known compounds and of all newly synthesized compounds are provided. The material is available free of charge via the Internet at http://pubs.acs.org

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