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Solid-Phase Selenium-Catalyzed Selective Allylic Chlorination of Polyprenoids: Facile Syntheses of Biologically Active Terpenoids

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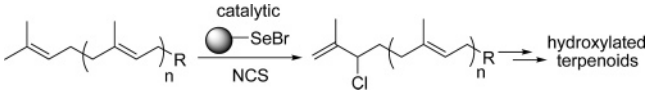
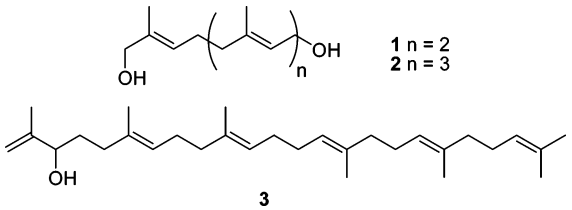


Regioselective halogenation of the terminal isopropylidene unit of different acyclic polyolefinic polyprenoids (farnesyl acetate, geranylgeranyl acetate, squalene, etc.) using NCS/catalytic polymer-supported selenenyl bromide is described; good to excellent yields are obtained (68−96%). The first applications of this protocol include the concise synthesis of bioactive terpenoids **1**−**3**.

The employment of acyclic polyprenoids possessing different olefinic double bonds as building blocks for the construction of bioactive molecules has constituted the basis of a number of synthetic strategies, among which biomimetic cyclizations are worth underlining.[1] Additionally, some hydroxylated polyprenoids can be considered as interesting synthetic targets, such as the bioactive terpenoids **1**−**3**. 12-Hydroxyfarnesol (**1**) is a synthetic compound which has been reported to possess interesting anti-ulcer activities;[2] 16-hydroxygeranylgeraniol (**2**) is a natural compound isolated from *Boletinus cavipes*, presenting a potent activity inhibitory of the superoxide anion generation in macrophage cells[3] and an antimicrobial activity against *Helicobacter pylori*;[4] and the squalene hydroxyderivative **3** is a natural product isolated from the plant *Croton hieronymi*.[5]



3

Both the generation of compounds as **1**−**3** and, in most of cases, the synthetic use as starting materials of simple acyclic terpenoids involve the selective functionalization of the terminal isopropylidene unit located in the extreme of the molecule, opposite to the one usually functionalized in this kind of molecules. This requires discrimination between two or more trisubstituted double bonds possessing a very similar electronic distribution, which poses a serious synthetic problem.

A number of synthetic methodologies have been published trying to overcome this problem. Considering the protocols oriented to obtain the corresponding epoxide, moderate results are obtained in the selective formation of bromohydrins,[6] whereas the asymmetric dihydroxylation process has proven to give better selectivities.[7] Allylic functionalization has been achieved by using either SeO_2 or Pd(II) complexes,[8] but these strategies give poor results when more than two double bonds are involved. Allylic chlorination using gaseous chlorine[9] at reflux in apolar solvents leads to the formation of chloro derivatives via an ene-type reaction. A method for the efficient allylic chlorination of monoolefins using NCS and catalytic PhSeCl has been reported recently,[10] a protocol based on previous works by Sharpless et al. which used NCS and diphenyl diselenide.[11]

Solid-phase stoichiometric or catalytic oxyselenenylation−deselenenylation reactions using polymer-supported selenium reagents have been reported recently.[12] Despite the recognized environmentally friendly nature of this solid-phase protocol, where the selenocatalyst is entirely separated by filtration of reaction mixture, there are no reports to date[13] on the application of this technique to the selective allylic chlorination of polyenes.

Continuing with our interest in the synthesis of bioactive terpenoids from acyclic polyprenic synthons,[14] we present in this work our results on the allylic chlorination of a series of

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(1) (a) Ho, T.-L. In *Carbocycle Construction in Terpene Synthesis*; VCH Publishers: New York, 1988. (b) Corey, E. J.; Cheng, X.-M. In *The logic of Chemical Synthesis*; Wiley & Sons: New York, 1989.

(2) Sato, A.; Nakajima, K.; Kuwana, N.; Takahara, Y.; Kijima, S.; Abe, S.; Yamada, K. Br. Pat. GB 2068370, 1981.

(3) Kamo, T.; Sato, K.; Sen, K.; Shibata, H.; Hirota, M. *J. Nat. Prod.* **2004**, *67*, 958−963.

(4) Tago, K.; Minami, E.; Masuda, K.; Akiyama, T.; Kogen H. *Bioorg. Med. Chem.* **2001**, *9*, 1781−1791.

(5) Catalán, C. A. N.; De Heluani, C. S.; Kotowicz, C.; Gedris, T. E.; Herz, W. *Phytochemistry* **2003**, *64*, 625−629.

(6) (a) Van Tamelen, E. E.; Sharpless, K. B.; Eugene, E. *Tetrahedron Lett.* **1967**, *28*, 2655−2659. (b) Van Tamelen, E. E.; Nadeau, V. *J. Am. Chem. Soc.* **1967**, *89*, 176−177.

(7) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768−2771. (b) Vidari, G.; Dapiaggi, A.; Zanoni, G.; Garlaschelli, L. *Tetrahedron Lett.* **1993**, *34*, 6485−6488. (c) Xu, D.; Park, C. Y.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *16*, 2495−2498. (d) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109−12110.

(8) El Firdoussi, L.; Baqqa, A.; Allaoud, S.; Ait Allal, B.; Karim, A.; Castanet, Y.; Mortreux, A. *J. Mol. Catal.* **1998**, *135*, 11−22.

(9) Mignani, G.; Grass, J. P.; Chabardes, P.; Morel, D. *Tetrahedron Lett.* **1992**, *33*, 495−498.

(10) Tunge, J. A.; Mellegaard, S. R. *Org. Lett.* **2004**, *6*, 1205−1207.

(11) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4204−4208. For more details of **6**, see Supporting Information.

(12) (a) Nicolau, K. C.; Pastor, J.; Barluenga, S.; Wissinger, N. *Chem. Commun.* **1998**, 1947−1948. (b) Fujita, K.; Taka, H.; Ikeda, Y.; Taguchi, Y.; Fujie, K.; Saeki, T.; Sakuma, M. *Synlett* **2000**, 1509−1511. (c) Nicolau, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q. Barluenga, S. Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.

(13) For examples of selenium-based approaches for solid-phase synthesis, see: Uehlin, L.; Wirth, T. *Org. Lett.* **2001**, *3*, 2931−2938 and references cited therein.

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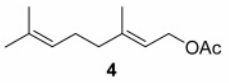
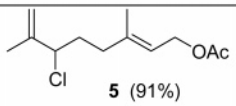
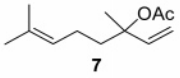
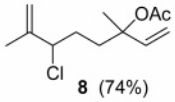
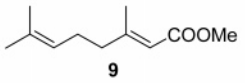
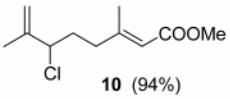
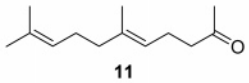
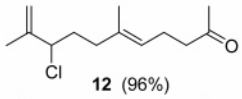
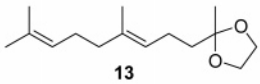
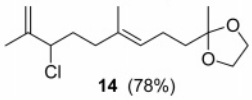
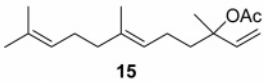
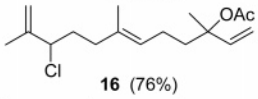
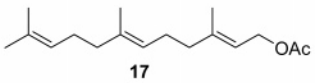
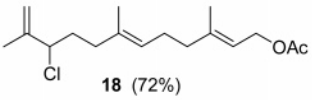
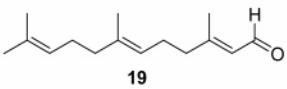
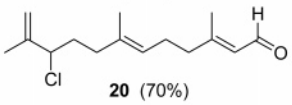
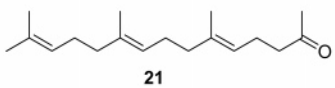
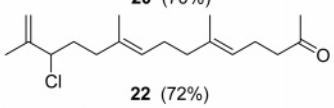
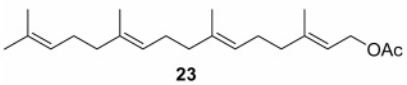
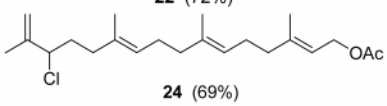
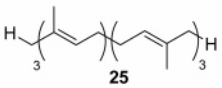
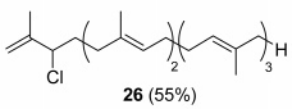
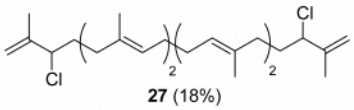
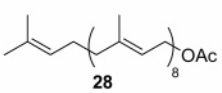
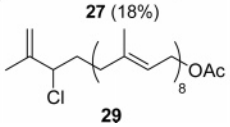
TABLE 1. Allylic Chlorination of Polyolefinic Polyprenoids Using NCS/Catalytic Polymer-Supported Selenenyl Bromide

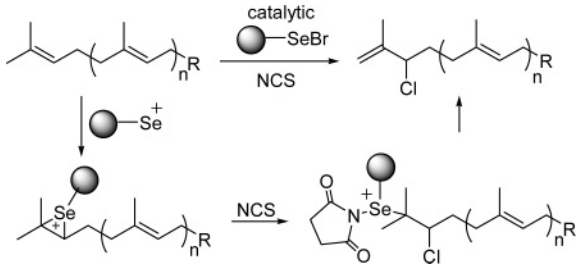
Entry	Compound	Time	NCS (equiv)	SeBr (equiv)	Product (yield %) [a,b]
1	 **4**	6 h	1.1	0.025	 **5** (91%)
2	**4**	4 h 50 min	1.1	0.05	**5** (93%)
3	**4**	5 h 20 min	2.2	0.02	**5** (85 %)
4	 **7**	4 h 40 min	1.1	0.05	 **8** (74%)
5	 **9**	5 h 30 min	1.1	0.05	 **10** (94%)
6	 **11**	3 h 30 min	1.1	0.05	 **12** (96%)
7	 **13**	5 h 30 min	1.1	0.05	 **14** (78%)
8	 **15**	5 h 20 min	1.1	0.05	 **16** (76%)
9	 **17**	3h 50 min	1.1	0.05	 **18** (72%)
10	 **19**	8 h	1.1	0.06	 **20** (70%)
11	 **21**	4 h 35 min	1.1	0.06	 **22** (72%)
12	 **23**	3 h 15 min	1.1	0.06	 **24** (69%)
13	 **25**	6 h 35 min	1.1	0.05	 **26** (55%)  **27** (18%)
14	 **28**	5 h 50 min	1.1	0.05	 **29**

[a] Isolated yield after column chromatography except for entries 13 and 14. [b] Vinylic chlorides analogous to **6** were easily detected by ^{1}H NMR in minor quantities in all reactions.

easily available polyolefinic polyprenoids (Table 1) using NCS and catalytic solid-supported selenenyl bromide with the aim of contributing to the search for easier and more selective ways of functionalizing these compounds. An increase in the efficiency of this transformation would permit widening substantially its use and applications. As result of the analysis of the most likely mechanism of these allylic chlorinations,[10] it was envisioned that the combined effects of the relatively big size of the electrophile (polymer-supported-Se$^+$), together with a minimum concentration of this species in the reaction medium, could lead to a position selectivity for the terminal isopropylidene group in polyolefinic polyprenoids, on the basis of its

(14) (a) Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074−4078. (b) Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Valdivia, M. V. *Org. Lett.* **2002**, *4*, 1379−1382. (c) Justicia, J.; Rosales, A.; Buñuel, E.; Oller-López, J. L.; Valdivia, M. V.; Häidour, A.; Oltra J. E.; Barrero, A. F.; Cárdenas, D.; Cuerva J. M. *Chem. Eur. J.* **2004**, *10*, 1778−1788.

SCHEME 1. General Approach



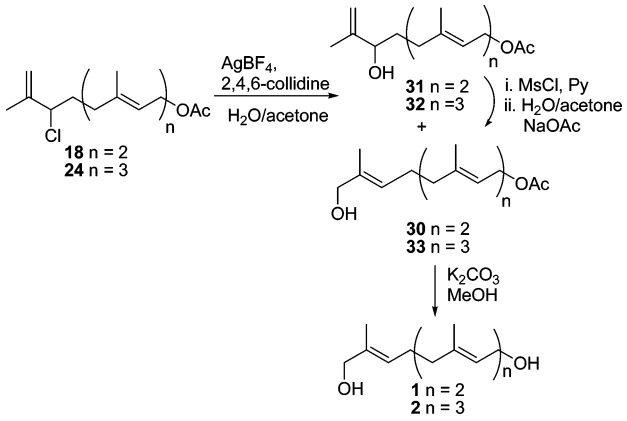
lesser steric demand (Scheme 1). Achieving success with this selective functionalization plan would imply having easy access to otherwise difficult to generate allyl chloro derivatives, which could be either used directly in coupling reactions or be transformed in other derivatives as allylic hydroxylated polyprenoids. Furthermore, this derivatization might further enable us to accomplish asymmetric transformations, such as the Sharpless asymmetric epoxidation protocol.

To test this idea, geranyl acetate (**4**) was made to react with 1.1 equiv of NCS and 0.025 equiv of polymer-supported selenenyl bromide in DCM (Table 1, entry 1). The reaction was completed after 6 h, and a 91% yield of secondary allylic chloride **5** was obtained. In addition, minor quantities of (2*E*)-6-chloro-3,7-dimethylocta-2,6-dienyl acetate (**6**) were also found.[11] This result shows a remarkable selectivity toward the double bond C(6)−C(7) and also corroborates the regioselectivity of the process toward the secondary isopropenyl chloride. The influence of the quantities of NCS and selenium reagent on the process was then tested (Table 1, entries 2 and 3). The best yield (93%) was found when 0.05 equiv of organoselenium resin was used. These conditions were adopted for the rest of the experiments carried out. With molecules possessing two double bonds (Table 1, entries 1−7), good to excellent yields (74−96%) and selectivities were found, the reaction being compatible with tertiary acetates, unsaturated esters, ketones, or ketals. In molecules where one of the double bonds is affected by an electron-withdrawing group, stereoelectronic effects could be argued to account for the selectivity observed.

However, when geranylacetone **11** (Table 1, entry 6) or its ketal derivative **13** (Table 1, entry 7) were used as substrates, the discrimination in favor of the terminal double bond can be rationalized only by considering steric reasons, excluding electronic considerations. This fact suggests that this reaction could reasonably work with molecules presenting a higher number of double bonds. Gratifyingly, this conjecture proved to be right, and polyprenoids possessing 3 or 4 trisubstituted double bonds also reacted satisfactorily (Table 1, entries 9−12). The results obtained with farnesyl acetate (**17**), farnesal (**19**), and geranylgeranyl acetate (**23**) (72, 70, and 69% yield, respectively, of the corresponding allylic chloride) deserve underlining. In fact, the yield afforded in the allylic chlorination of **23** is higher than the one obtained by using other selective functionalizations, such as the asymmetric dihydroxylation employing the Noe−Lin catalyst.[15a] Comparable results can only be achieved with the Corey−Zhang ligand.[15b] Attention was then turned to squalene (**25**), and when it was subjected to the above-mentioned optimized experimental conditions (Table 1, entry 13), a 55% of the corresponding monochloro derivative

(15) (a) Corey, E. J.; Noe, M. C.; Lin, S. *Tetrahedron Lett.* **1995**, *36*, 8741−8744. (b) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211−3214.

SCHEME 2. Synthesis of 1 and 2



26 together with a 18% of dichloro derivative **27** and a 14% of unaltered starting material were obtained.[16] An acceptable yield of **27** (70%) was obtained by increasing the quantity of NCS (2.2 equiv) used. Other selective functionalizations reported for squalene[17] are less efficient that the one herein described.

We faced then the challenge of functionalizing selectively solanesyl acetate (**28**), a molecule presenting nine trisubstituted double bonds. Thus, when **28** was made to react with NCS/polymer-bound selenenyl bromide for 2 h, a 60% of a 3:1 mixture favoring the terminal chlorinated product **29** against internal functionalizated derivatives was found, together with a 20% of recovered starting material (Table 1, entry 14).[18] Efforts to further transform the starting material led to a loss of position selectivity.

With these results in mind, we anticipated that different triterpenoids such as **1**−**3** could be easily synthesized using this catalytic protocol. The synthesis of **1** has been accomplished from chloro derivative **18** via a simple two-step sequence (Scheme 2).

Thus, $AgBF_4$-mediated hydrolysis of **18** led to a 40% yield of the corresponding primary hydroxy derivative **30**, together with an additional 45% yield of the secondary alcohol **31**. The efficiency of this process was improved by conversion of **31** into **30** in 41% yield via mesylation and subsequent hydrolysis with acetone/H_2O. Saponification of the acetate with K_2CO_3/MeOH afforded the desired diol **1**. Following the same sequence, compound **2** was obtained from geranylgeranyl acetate with a global yield of 37%, which means a considerable improvement of the only previous synthesis of this compound.

Similarly, triterpene **3** was obtained for the first time from squalene (**25**) in a 32% yield (Scheme 3).

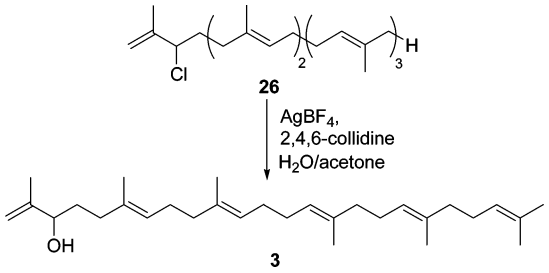
In summary, we have established the conditions for an easy and highly selective position functionalization toward the terminal double bond of a series of easily available terpenoids. This methodology is compatible with the presence of different functional groups in the starting material, allowing easy access to functionalized synthons that can be employed in numerous synthetic operations. The use of a polymer-supported selenium reagent, with the well-recognized advantages associated to it,

(16) Yields obtained by conversion into the corresponding hydroxy derivatives. With lesser dregrees of conversion, the selectivity of the reaction toward **26** increases. Thus, a 5:1 ratio of **26**/**27** was found after only 10 min of reaction time, recovering 80% of squalene unaltered.

(17) Crispino, G. A.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 4273−4274.

(18) Yields obtained by conversion into the more stable acetoxy derivative **29a**. For more details of **29a**, see the Experimental Section.

SCHEME 3. Synthesis of 3



constitutes an additional plus of this protocol. This reaction has been applied to the rapid and efficient synthesis of three interesting hydroxyterpenoids.

Experimental Section

General Procedure for Allylic Chlorination of Polyolefinic Polyprenoids Using NCS/Polymer-Supported Selenelyl Bromide. Commercially available solid-supported selenenyl bromide (0.05 mmol) was dissolved in DCM (6 mL). To this solution was added the corresponding acyclic polyolefinic polyprenoid (1.0 mmol) at rt. To this mixture was added *N*-chlorosuccinimide (1.1 mmol) (TLC monitoring). The solution was concentrated and then suspended with diethyl ether. The organic layer was decanted from the solid, washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding secondary allylic chloro derivative.

(2*E*,6*E*)-10-Hydroxy-3,7,11-trimethyldodeca-2,6,11-trienyl Acetate (31). (2*E*,6*E*)-10-Chloro-3,7,11-trimethyldodeca-2,6,11-trienyl acetate (**18**) obtained by regioselective chlorination of farnesyl acetate (750 mg, 2.51 mmol) was dissolved in acetone (25 mL), and then H_2O (50 mL), 2,4,6-collidine (1.34 mL, 10.0 mmol), and $AgBF_4$ (973 mg, 5.0 mmol) were added. The resulting mixture was refluxed at 60−70 °C for 1 h (TLC monitoring). Then, acetone was removed under reduced pressure and the residue was extracted with EtOAc (3 × 20 mL). The organic layer was washed with 2 N HCl and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, and the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2.5:1) on silica gel to afford **30**[19] (280 mg, 40%) and **31** (312 mg, 45%). Data for **31**: IR (film) 3453, 2967, 2938, 2856, 1740, 1446, 1382, 1367, 1234, 1023, 954, 898 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.54 (3H, s), 1.55−1.68 (2H, m), 1.63 (3H, s), 1.66 (3H, s), 1.85−2.12 (6H, m), 1.98 (3H, s), 3.96 (1H, t, J = 6.5 Hz), 4.51 (2H, d, J = 7.1 Hz), 4.76 (1H, q, J = 1.5 Hz), 4.86 (1H, t, J = 0.9 Hz), 5.07 (1H, dt, J = 6.8 Hz, J = 1.2 Hz), 5.28 (1H, tq, J = 7.1 Hz, 1.2 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 16.0, 16.5, 17.7, 21.1, 26.1, 33.2, 35.7, 39.5, 61.5, 75.6, 111.0, 118.5, 124.2, 135.2, 142.1, 147.6, 171.2; HRFABMS calcd for $C_{17}H_{28}O_3Na$ $[M + Na]^+$ 303.1936, found 303.1934. To a solution of **31** (145 mg, 0.51 mmol) in 5 mL of pyridine at 0 °C was added DMAP (cat.). After 10 min, MsCl (0.88 mL, 3.0 mmol) was added. The reaction mixture was stirred for 1 h, quenched with saturated aqueous $NaHCO_3$, extracted with *t*-BuOMe, washed with 1 N HCl, $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was dissolved in acetone (5 mL) and H_2O (4 mL), and then NaOAc (100 mL) was added. The mixture was heated at reflux for 2 h. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford **31** (53 mg, 38%) and **30** (57 mg, 41%), improving in this way the efficiency of the process.

(2*E*,6*E*,10*E*)-12-Hydroxyfarnesol (1). Saponification of **30** (30 mg, 0.11 mmol) with K_2CO_3 (45 mg) in MeOH (4 mL) was achieved in 20 min at rt to give **1**[20] (26 mg, 99%).

(2*E*,6*E*,10*E*)-14-Hydroxy-3,7,11,15-tetramethylhexadeca-2,6,10,15-tetraenyl Acetate (32). According to the procedure described for the preparation of **30** and **31**, the resulting crude from treating **24** with $AgBF_4$ was purified by column chromatography (hexane/*t*-BuOMe, 2.5:1) on silica gel to afford **33**[21] (37%) along with **32** (39%). **Data for 32**: IR (film) 3430, 2924, 2854, 1740, 1651, 1447, 1383, 1233 and 1024 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.55−1.65 (2H, m), 1.59 (3H, s), 1.61 (3H, s), 1.70 (3H, s), 1.72 (3H, s), 1.76 (1H, s, O*H*), 1.90−2.15 (10H, m), 2.04 (3H, s), 4.03 (1 H, t, J = 6.4 Hz), 4.58 (2H, d, J = 7.1 Hz), 4.83 (1H, s), 4.93 (1H, s), 5.09 (1H, t, J = 6.3 Hz), 5.14 (1H, t, J = 6.4 Hz), 5.34 (1H, dt, J = 6.3, 1.0 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 16.0, 16.5, 17.7, 21.1, 26.2, 26.6, 33.2, 35.8, 39.5, 39.6, 61.5, 75.6, 111.0, 118.3, 123.8, 124.7, 134.8, 135.4, 142.3, 147.5, 171.2; HRFABMS calcd for $C_{22}H_{36}O_3Na$ $[M + Na]^+$ 371.2562, found 371.2571. According to the procedure described for the conversion of **31** into **30**, the transformation of **32** into **33** via mesylation and subsequent hydrolysis with acetone/H_2O proceeded in a 45% yield.

16-Hydroxygeranylgeraniol (2). Saponification of **33** (53 mg, 0.15 mmol) with K_2CO_3 (52 mg, 0.38 mmol) in MeOH (6 mL) was achieved in 20 min at rt to give **2**[4] (45 mg, 98%).

(6*E*,10*E*,14*E*,18*E*)-2,6,10,15,19,23-Hexamethyltetracosa-1,6,10,14,18,22-hexaen-3-ol (3). According to the procedure described for the preparation of **30** and **31**, the resulting crude from treating the mixture of **26** and **27** (3:1 ratio) with $AgBF_4$ was purified by column chromatography (hexane/*t*-BuOMe, 2.5:1) on silica gel to afford **3**[5] (26%) and the primary alcohol (2*E*,6*E*,10*E*,-14*E*,18*E*)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaen-1-ol[22] (20%) along with (2*E*,6*E*,10*E*,14*E*,18*E*)-2,6,10,15,-19,23-hexamethyltetracosa-2,6,10,14,18,23-hexaene-1,22-diol (9%) and (2*E*,6*E*,10*E*,14*E*,18*E*,22*E*)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaene-1,24-diol[4] (6%). **Data for (2*E*,6*E*,10*E*,14*E*,18*E*)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,23-hexaene-1,22-diol:** IR (film) 3387, 2922, 2855, 1658, 1446, 1382 and 1014 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 1.55−1.65 (2H, m), 1.59 (12H, s), 1.65 (3H, s), 1.71 (3H, s), 1.93−2.15 (18H, m), 3.98 (2H, s), 4.03 (1H, t, J = 6.3 Hz), 4.83 (1H, t, J = 1.6 Hz), 4.93 (1 H, s), 5.13 (4H, m), 5.38 (1 H, dt, J 6.9, 1.2 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 13.8, 16.1, 17.7, 26.4, 26.7, 28.4, 33.3, 35.8, 39.4, 39.8, 39.8, 69.1, 75.7, 111.0, 124.5, 124.5, 124.7, 124.9, 126.3, 134.6, 134.7, 134.8, 135.1, 135.1, 147.6; HRFABMS calcd for $C_{30}H_{50}O_2Na$ $[M + Na]^+$ 465.3709, found 465.3694.

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **1**−**3**, **6**, **10**, **12**, **16**, **18**, **24**, **29a**, **31**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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