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The prenyl group: a versatile hydroxy protecting group, removable chemoselectively under mild conditions

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Abstract—Iodine in dichloromethane (in the presence of 3 Å molecular sieves for acid-sensitive substrates) and 2,3-dichloro-5,6-dicyanoquinone (DDQ) in dichloromethane–water (9:1) are mild and efficient methods to cleave prenyl ethers. These reaction conditions are compatible with the presence of other protecting groups such as acetals, acetates, allyl, benzyl and TBDPS groups. Exposure of aryl prenyl ethers to iodine led to the formation of 3-iodo-2,2-dimethylchroman derivatives in acceptable yields via a tandem Friedel–Crafts/iodocyclization reactions. Facile one-step transformation of two iodinated dimethylchroman derivatives allowed the synthesis of natural flavanoids among them: zanthoxylol, an anti-sickling agent. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Organic synthesis has not yet matured to the point where protective groups are not needed for the synthesis of natural and unnatural products and so selective protection, and more importantly, deprotection of functional groups still play a central role in the success of the synthesis of complex natural products.

One of the most present functional group in natural products is the hydroxy group for which a number of protecting groups has been designed. However, because of the increasing complexity of the molecules synthesized and the emergence of new fields in organic synthesis such as supported-oligosaccharide synthesis,[1] new protecting groups with modulated reactivity and new techniques of cleavage of existing protecting groups are needed.

In connection with a program devoted to the development of new safety-catch protecting groups,[2] a hydroxy protecting group stable under both acid and base conditions and cleaved under neutral conditions was needed. Among the numerous existing protecting groups, the allyl group does fulfill acid–base stability requirements but none of the several deprotecting methods for this group were satisfactory for our purpose.[3]

Next, we focused our attention to a related allyl group: the 3-methylbut-2-enyl (prenyl) group in which surprisingly the potentialities as an OH protecting group was almost completely unexplored. Indeed, only three methods of cleavage of prenyl ethers have been described.[4] Two of them used drastic conditions (*t*-BuOK[4a] or $TiCl_4$, *n*-Bu_4NI[4c]) and are not compatible with acid or base sensitive functionalities. The third one employed $Yb(OTf)_3$,[4b] a mild Lewis acid catalyst, which anyhow is able to cleave acid-sensitive protecting groups.[5]

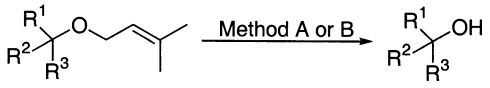
We have recently reported in preliminary accounts two mild and selective methods to regenerate alcohols from prenyl ethers (Scheme 1).[6]

We now reported, in full details, studies of these methods of prenyl ethers deprotection, particularly of their chemoselectivity against other protecting groups and probable mechanisms involved in these processes.

2. Results and discussion

2.1. Deprotection of prenyl ethers with iodine

Inspired by the report of Cossy and co-workers about a method for the deprotection of prenyl esters,[7] the prenyl ether of diacetone glucose **1a** was treated at room temperature with iodine in cyclohexane. Disappointingly, TLC



Method A: I_2, CH_2Cl_2, 3A molecular sieves
Method B: DDQ, CH_2Cl_2-H_2O (9:1)

Scheme 1.

Keywords: DDQ; iodine; protecting groups; prenyl ethers; chromans.
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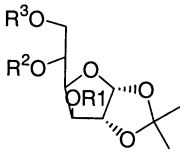
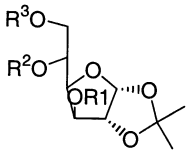
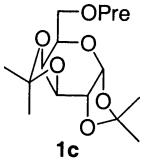
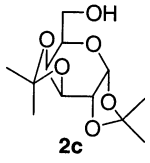
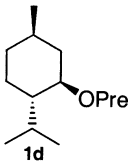
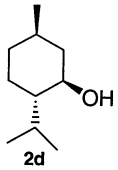
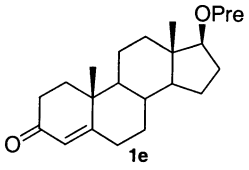
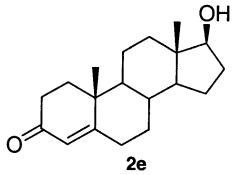
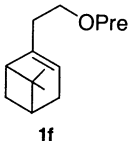
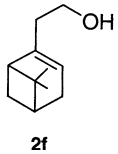
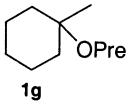
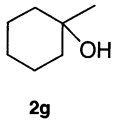
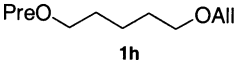
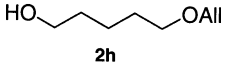
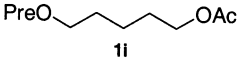
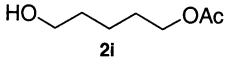
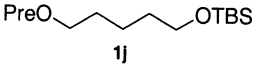
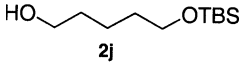
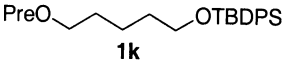
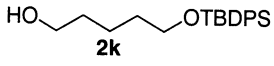
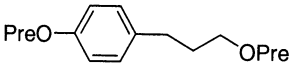
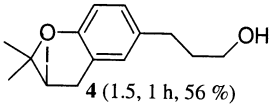
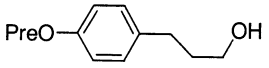
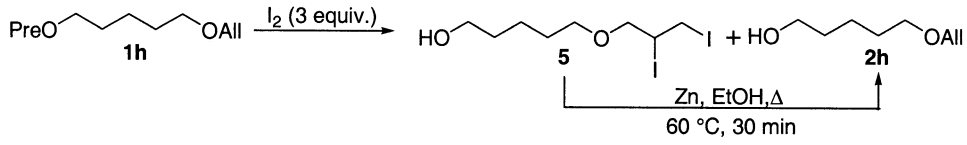
Table 1. Cleavage of prenyl ethers with iodine or 2,3-dichloro-5,6-dicyanoquinone

Substrate	I_2	Product (equiv., time, yield)	DDQ
			
1a R^1=Pre, R^2, R^3=CMe_2 **1b** R^1=Bn, R^2, R^3=Pre	(1.5, 5 h, 61%) (3, 3 h, 50%) (1.2, 2 h, 54%)	**2a** R^1=H, R^2, R^3=CMe_2 **2b** R^1=Bn, R^2, R^3=H **3b** R^1=Bn, R^2=H, R^3=Pre	(1.2, 9 h, 65%) (1.2, 4 h, 68%) (1, 4 h, 33%)
 **1c**	(1.5, 8 h, 72%)	 **2c**	(1.2, 4 h, 89%)
 **1d**	(1.5, 1 h, 92%)	 **2d**	(1.2, 15 min, 86%)
 **1e**	(3, 3 h, 79%)	 **2e**	(1.2, 0.75 h, 89%)
 **1f**	(1.2, 0.5 h, 0%)	 **2f**	(1.2, 1.5 h, 78%)
 **1g**	(1.5, 1 h, 75%)	 **2g**	(1.2, 1.5 h, 72%)
 **1h**	(3, 1.5 h, 80%)	 **2h**	(1.2, 3 h, 86%)
 **1i**	(1.5, 1 h, 77%)	 **2i**	(1.2, 4 h, 94%)
 **1j**	(1.5, 4 h, 22%)	 **2j**	(1,2,3 h, 80%)
 **1k**	(2, 3 h, 70%)	 **2k**	(1.2, 3 h, 83%)
 **1l**	 **4** (1.5, 1 h, 56 %)		 **2l** (1.2, 2 h, 36 %)

showed the presence almost exclusive of polar compounds. Switching from cyclohexane to toluene permitted the isolation of diacetone glucose **2a** in 32% yield after heating 4 h at 70°C. In more polar solvents (CH_2Cl_2, CH_3CN), the disappearance of the starting material was much faster (1 versus 24 h) but still polar compounds were formed.

Assuming that during the cleavage of prenyl ethers with iodine an acid species might be generated (HI) deprotecting acetal functions of **1a**, acid scavengers were added prior to iodine. Addition of 1 equiv. of Et_3N inhibited completely the cleavage reaction whereas sodium carbonate (2 equiv.) slowed it down suggesting that HI



Scheme 2.

was produced during the cleavage and catalyzed this process.

In the presence of 3 Å molecular sieves (a known hydrogen halides scavenger)[8] the deprotection of prenyl ether **1a** in CH_2Cl_2 proceeded at room temperature at a reasonable rate (5 h) to give diacetone glucose in 61% yield. The use of iodine in CH_2Cl_2, in the presence of 3 Å molecular sieves for acid-sensitive substrates, was examined on diversely funtionalized substrates and the results of this study are summarized in Table 1.

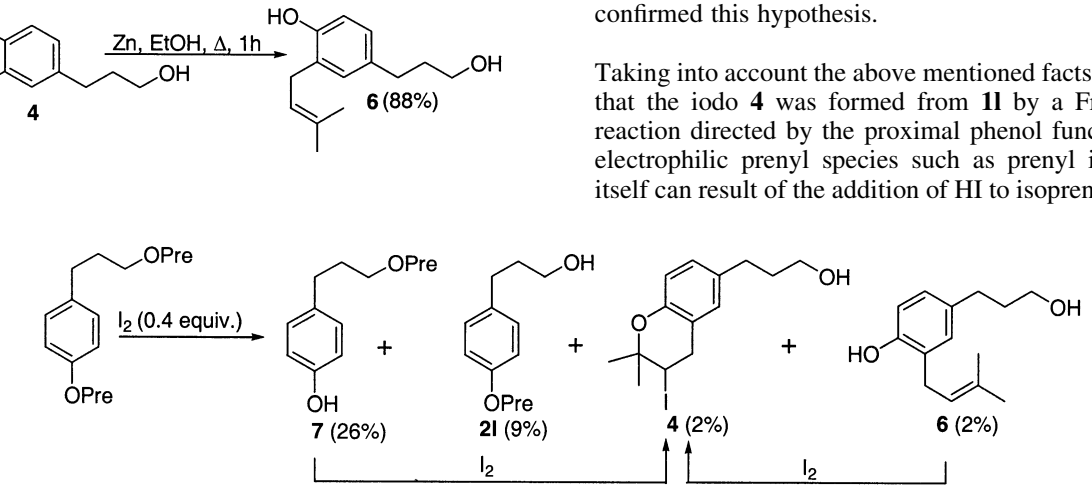
Firstly, exposure of the diprenyl ether **1b** to 1.2 equiv. of iodine led to the formation of the 5-*O*-deprotected compound **3b** in 54% yield; the 6-*O*-deprotected compound was not observed by TLC. Conversely, treatment of **1b** with 1 equiv. of DDQ gave approximately an equal mixture of the two monoprotected compounds along with some of the dideprotected product **2b**.

Protecting groups such as acetonides (**1a**–**1c**), acetates (**1i**), benzyl (**1b**) and *t*-butyldiphenylsilyl (**1k**) groups or the conjugated ketone function of **1e** were unaffected in the reaction conditions. In the case of compound **1h** bearing an allyl group, the desired compound **2h** was obtained along with the *vic*-diiodo compound **5** (ratio **2h/5**=1/3). Treatment of the mixture of compounds **2h** and **5** with zinc gave **2h** in 80% overall yield (Scheme 2). Unfortunately, even in the presence of molecular sieves, the *O*-prenyl group of **1j** could not be removed selectively in the presence of a *t*-butyldimethysilyl group. Treatment of prenyl ether **1f** with iodine, at −10°C, did not give the expected nopol **2f** but several unidentified products. The known facile skeletal rearrangement of α-pinene derivatives in the presence of electrophiles may explain this result.[9]

Interestingly, aryl prenyl ether **1l** in the presence of 1.5 equiv. of iodine gave the 3-iodo-2,2-dimethylchroman derivative **4** in an acceptable yield. Ring opening of the β-iodo cyclic ether unit of **4** via the Boord reaction (zinc in boiling toluene) led cleanly to natural anti-sickling agent zanthoxylol in 88% yield (Scheme 3).[10]

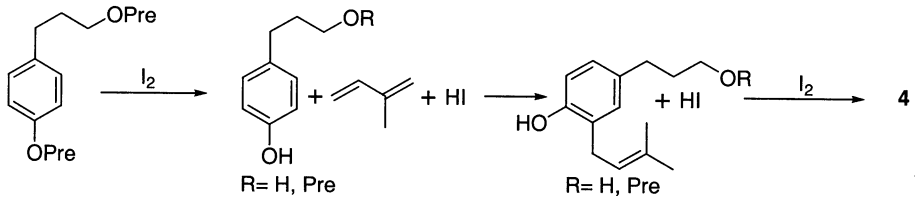
In order to clarify the reaction pathway **1l**→**4** and to isolate the intermediates of the cyclization reaction, the reaction was carried out with only 0.4 equiv. of iodine. Four compounds were isolated (Scheme 4). Formation of **7**, major product of the reaction and corresponding to the cleavage of the aryl prenyl ether, excluded that *ortho*-prenyl phenol **6**, the immediate precursor of **4**, was formed via a [1,3]-sigmatropic rearrangement.[11] Exclusive formation of the iodo **4** obtained by treatment of **7** by an excess of iodine confirmed this hypothesis.

Taking into account the above mentioned facts, we presume that the iodo **4** was formed from **1l** by a Friedel–Crafts reaction directed by the proximal phenol function with an electrophilic prenyl species such as prenyl iodide which itself can result of the addition of HI to isoprene,[12] followed

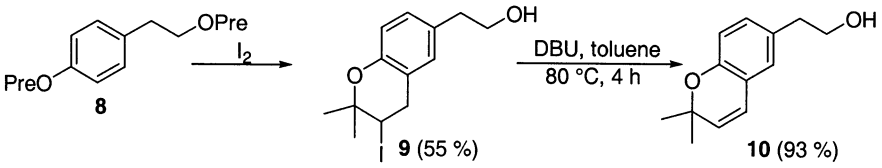


Scheme 3.

Scheme 4.



Scheme 5.



Scheme 6.

by iodocyclization (**6** cyclized to **4** in the presence of iodine) (Scheme 5).[13]

This reaction of aryl prenyl ethers with iodine was applied to the synthesis of natural product **10**, recently isolated from the stems of *Paramignya griffithii*, used in Thailand for the treatment of nose infections.[14] Bis-*O*-prenylation of commercially available 2-(4-hydroxyphenyl)ethanol followed by exposure to iodine and double bond formation induced by DBU in hot toluene furnished the 2,2-dimethylchromene **10** in 49% overall yield (Scheme 6).

2.1.1. Mechanistic studies of the cleavage of prenyl ethers by iodine. As mentioned earlier in this article, addition of bases to the reaction mixture inhibits or retards the deprotection of prenyl ethers suggesting that an acid species (HI) is necessary for the cleavage to occur. Moreover, in contrast to 3-*O*-allyl diacetone glucose which, in the presence of 1.5 equiv. of iodine, gave isolable vicinal diiodides,[15] no addition product of iodine to the double bond of prenyl ether **1a** was observed by TLC, even at −78°C, precluding that a *vic*-diiodo could be an intermediate in the cleavage of prenyl ethers. We next wondered if a stoechiometric amount of iodine was necessary. It turned out not to be the case because the deprotection of the prenyl ether of menthol **1d** could be done with 0.4 equiv. of iodine at room temperature in 89% yield, albeit at the expense of the rate of the reaction (4 h 30 versus 15 min with 1.5 equiv. of I_2).

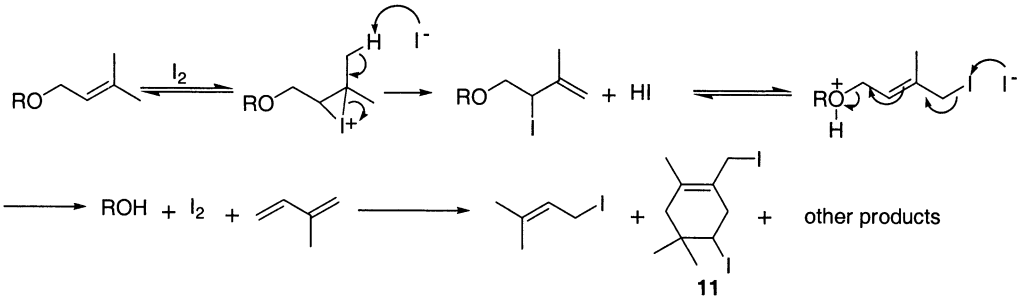
Another experiment to go insight the mechanism consisted to carry out the reaction with *O*-prenyl menthol **1d**, in an NMR tube using $CDCl_3$ as solvent. ^{13}C NMR showed clearly the five carbon signals of the prenyl iodide (δ= 4.0, 17.4, 25.8, 122.1, 138.8 ppm)[16] which represents 15–20 mol% in comparison with menthol. Along with some minor products, ^{13}C and ^{1}H NMR also revealed the presence of the unstable diiodo **11** (5–7 mol%) (Scheme 7) which could be obtained in almost pure form by chromatography on silica gel.

Armed with these information and those concerning the probable mechanism of formation of 2,2-iodochroman **4** from **1l** (Scheme 5), a possible mechanism for the iodine catalyzed-cleavage of prenyl ethers is outlined in Scheme 7.

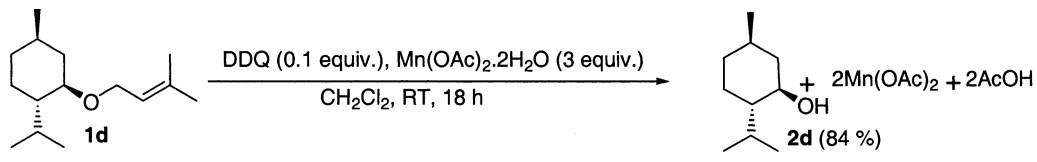
2.2. Oxidative cleavage of prenyl ethers by DDQ

If the method of deprotection of prenyl ethers by iodine gave satisfactory results on most subtrates, it is not compatible with very acid-sensitive functions such as TBS and with substrates which are reactive with electrophiles such as phenols, terpenes. So, we decided to look for another more general and milder method.

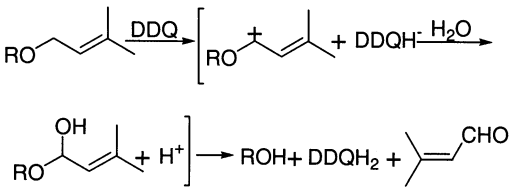
From the literature, we learned that allylic ethers are easily oxidized by 2,3-dichloro-5,6-dicyanoquinone (DDQ) to corresponding carbonyl compounds and alcohols.[17] Confident that DDQ can oxidize prenyl ethers as well, the *O*-prenyl ether of menthol **1d** was treated at room temperature, by 1.2 equiv. of DDQ in a mixture CH_2Cl_2–H_2O (9:1). After stirring for 30 min, TLC indicated the disappearance of the starting material and formation of two compounds with very close R_f. Separation of the two compounds on silca gel gave menthol in 86% along with volatile 3-methyl-2-butenal.



Scheme 7.



Scheme 8.



Scheme 9.

Then we tested the applicability of this method to functionalized substrates and the results of this study is summarized in Table 1. As shown in the Table, the reaction time is very dependent on the substrate varying from 45 min to 9 h. This method is compatible with substrates containing protecting groups such as acetonides (**1a**–**1c**), acetates (**1i**), benzyl (**1b**), *t*-butyldimethylsilyl (**1j**), *t*-butyldiphenylsilyl (**1k**) and allyl (**1h**) groups. In the latter case, the good selectivity was unexpected because it has been reported that under the same conditions, albeit in longer time, primary allyl ethers were cleaved.[17b] Exposure of **1l**, bearing an aryl ether, to DDQ gave the monoprotected compound **2l** in only 36% yield; no compound bearing a phenol function was detected. DDQ is known as a powerful oxidizing agent of phenols[18] and that may explained the low yield of the reaction.

Because DDQ is an expensive reagent and the removal of its corresponding hydroquinone is sometimes cumbersome, Sharma and co-workers developed a method which allowed the use of DDQ in catalytic amount (0.1 equiv.) in the presence of Mn^{3+} salts as a reoxidant.[19] Under these conditions, the *O*-prenyl ether menthol **1d** afforded menthol in 84% yield (Scheme 8). The yield of this protocol is similar of that using a stoechiometric amount of DDQ but the reaction time is longer (18 h versus 90 min).

Mechanistically, the oxidation/deprotection of prenyl ethers with DDQ must proceed by hydride abstraction from the activated methylene by DDQ followed by trapping the carbonium by water giving a hemiacetal which decomposes to give an alcohol, $DDQH_2$ and 3-methylbut-2-enal (Scheme 9).[20]

3. Conclusion

In summary, we have shown that prenyl ethers could be cleaved by I_2 or oxidatively by DDQ in the presence of a number of other commonly used protecting groups but are not applicable to aryl prenyl ethers. These mild conditions broaden the synthetic applications of prenyl ethers and the good chemoselectivity of these methods extends its utility as an orthogonal protecting group. Other applications of the prenyl group in organic synthesis are currently under studies.

4. Experimental

4.1. General procedures

^{1}H NMR spectra were recorded in $CDCl_3$ (δ_H=7.25) at ambiant probe temperature on a Bruker AC 200 (200 MHz) spectrometer. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS}=0), multiplicity (s=singulet, d=doublet, t=triplet, m=multiplet, br=broad); integration, coupling constant and interpretation). ^{13}C NMR spectra were recorded at ambiant probe temperature on a Bruker AC 200 (50.3 MHz) in $CDCl_3$ used as reference (δC=77.0). IR spectra were recorded on a Perkin–Elmer 298 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 141 polarimeter at the sodium D line (598 nm). Melting points were determined on a Büchi 530 apparatus and are uncorrected. Combustion analyses were performed by the Service de Microanalyse, CNRS, Solaize. Reagents and solvents were purified by standard means. Tetrahydrofuran was distilled from sodium wire/benzophenone and stored under a nitrogen atmosphere. Dichloromethane, dimethylformamide, pyridine and toluene were distilled from calcium hydride. Powdered 3 Å molecular sieves (Aldrich) was dried at 100°C for 10 h. All other chemicals were used as received.

4.2. General procedure for the preparation of prenyl ethers 1a–1g and 1l

To 1 mmol of the substrate dissolved in 3 mL of DMF, cooled to 0°C, were successively added prenyl bromide (0.18 mL, 1.5 equiv.; for **1b** and **1l** 3 equiv.) and NaH (60% dispersion in mineral oil, 0.048 g, 1.2 equiv., for **1b** and **1l** 2.4 equiv.). The reaction mixture was allowed to warm up to room temperature and the stirring was continued for 2 h. Excess of NaH was destroyed by MeOH and ether and water were added. The aqueous phase was extracted with ether and the combined organic layers were washed once with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel.

4.2.1. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(3-methyl-2-butenyl)-α-D-glucofuranose 1a. Ether–petroleum ether (1:4), 97% yield, oil, $[\alpha]_D^{20}=-20.6$ (*c* 2, $CHCl_3$) (lit.[21] $[\alpha]_D=-21.6$ (*c* 1, $CHCl_3$)). NMR data were identical with those described in the literature.[21]

4.2.2. 3-*O*-Benzyl-1,2-*O*-isopropylidene-5,6-di-*O*-(3-methyl-2-butenyl)-α-D-glucofuranose 1b. Obtained from 3-*O*-benzyl-1,2-isopropylidene-α-D-glucofuranose.[22] Ether–petroleum ether (1:3), 93%, oil, $[\alpha]_D^{20}=-33$ (*c* 3.4, $CHCl_3$). IR (film): 3080, 3060, 3020, 1670, 1585 cm^{-1}. ^{1}H NMR: 1.31 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.56 (dd, 1H, *J*=6 and 10.8 Hz, H-6), 3.78–4.14 (m, 6H, H-3, H-5, H-6, 3 C*H*$_2$–CH=C), 4.21 (dd, 1H, *J*=3 and 9.4 Hz, H-4), 4.32 (dd, 1H, *J*=7.8 and 10.8 Hz, C*H*$_2$–CH=C), 4.58 (d, 1H, *J*=3.7 Hz, H-2), 4.60 (d, 1H, *J*=11.6 Hz, ChaPh), 4.69 (d, 1H, CHbPh), 5.3 (brt, 1H, *J*=6.95 Hz, C*H*=CMe$_2$), 5.34 (brt, 1H, *J*=6.83 Hz, C*H*=CMe$_2$), 5.90 (d, 1H, *J*=3.7 Hz, H-1), 7.34 (brs, 5H, Ph). ^{13}C NMR: 18.0, 18.1, 25.8 (2C), 26.4, 26.8, 67.1, 67.9, 71.0, 72.1, 74.9, 79.2, 81.9, 82.0, 105.2, 111.7, 121.6, 121.7, 127.5 (2C), 127.8, 128.5 (2C), 136.3, 136.4, 137.8. Anal. calcd for $C_{28}H_{38}O_6$: C, 69.93, H, 8.58, O, 21.5. Found: C, 69.84, H, 8.64, O, 21.25.

4.2.3. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3-methyl-2-butenyl)-α-D-galactopyranose 1c. Ether–petroleum ether (1:4), 87%, oil, $[\alpha]_D^{20}=-73.5$ (*c* 1, $CHCl_3$). IR (film): 1660 cm^{-1}. ^1H NMR: 1.31 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.54 (dd, 1H, *J*=6.5 and 9.9 Hz, H-6), 3.63 (dd, 1H, *J*=6.1 and 10 Hz, H-6), 3.96 (dt, 1H, *J*=1.8 and 6.3 Hz, H-5), 4.02 (d, 2H, *J*=7 Hz, CH_2–CH=C), 4.27 (dd, 1H, *J*=1.8 and 7.9 Hz, H-4), 4.3 (dd, 1H, *J*=2.3 and 5 Hz, H-2), 4.58 (dd, 1H, *J*=2.3 and 7.9 Hz, H-3), 5.33 (brt, 1H, *J*=6.9 Hz, C*H*=CMe_2), 5.52 (d, 1H, *J*=5 Hz, H-1). ^{13}C NMR: 18.0, 24.5, 25.0, 25.8, 26.0, 26.1, 66.8, 67.8, 68.4, 70.67, 70.69, 71.2, 96.4, 108.5, 109.2, 121.3, 136.9. Anal. calcd for $C_{17}H_{28}O_6$: C, 62.17, H, 8.59, O, 29.23. Found: C, 62.08, H, 8.63, O, 29.34.

4.2.4. (1*R*,2*S*,5*R*)-Menthyl 3-methylbuten-2-yl ether 1d. Ether–petroleum ether (2:98), 92%, oil, $[\alpha]_D^{20}=-91.4$ (*c* 2, $CHCl_3$). IR (film): 1670 cm^{-1}. ^1H NMR: 0.77 (d, 3H, *J*=6.9 Hz, CH_3), 0.88 (d, 3H, *J*=6.6 Hz, CH_3), 0.92 (d, 3H, *J*=6.6 Hz, CH_3), 0.95–1.5 (m, 5H), 1.55–1.67 (m, 2H), 1.68 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.02–2.37 (m, 2H), 3.04 (td, 1H, *J*=4.2 and 10.4 Hz, C*H*OR), 3.82 (dd, 1H, *J*=7.1 and 11 Hz, C*Ha*–C=C), 4.1 (dd, 1H, *J*=7 and 11 Hz, C*Hb*–CH=C), 5.36 (brt, 1H, *J*=6.95 Hz, C*H*=CMe_2). ^{13}C NMR: 16.2, 18.0, 21.0, 22.4, 23.4, 25.5, 25.8, 31.7, 34.7, 40.6, 48.3, 64.8, 78.3, 121.9, 136.3. Anal. calcd for $C_{15}H_{28}O$: C, 80.29, H, 12.58, O, 7.13. Found: 80.01, H, 12.56, O, 7.18.

4.2.5. 17-β-(3-Methyl-2-butenyloxy)androst-4-en-3-one 1e. Ether–petroleum ether (1:1), 46% yield, crystalline solid: mp 64–65°C, $[\alpha]_D^{20}=+89.3$ (*c* 1.6, $CHCl_3$). IR (KBr): 1670, 1613 cm^{-1}. ^1H NMR: 0.8 (s, 3H, CH_3), 0.81–1.1 (m, 3H), 1.16 (s, 3H, CH_3), 1.2–1.62 (m, 7H), 1.63 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.9–2.12 (m, 4H), 2.15–2.5 (m, 4H), 3.31 (t, 1H, *J*=8.2 Hz, C*H*OR), 3.90 (q, 1H, *J*=7 and 11.45 Hz, C*Ha*–CH=C), 3.98 (q, 1H, *J*=7 and 11.5 Hz, C*Hb*–CH=C), 5.3 (brt, 1H, *J*=6.9 Hz, C*H*=CMe_2), 5.7 (brs, 1H, CO–C*H*=C). ^{13}C NMR: 11.7, 17.5, 18.1, 20.8, 23.4, 25.9, 28.2, 31.6, 32.9, 34.0, 35.5, 35.8, 37.8, 38.7, 42.9, 50.8, 54.0, 66.7, 88.3, 122.0, 123.9, 136.1, 171.3, 199.6. Anal. calcd for $C_{24}H_{36}O_2$: C, 80.85, H, 10.18, O, 8.97. Found: C, 80.7, H, 10.24, O, 8.91.

4.2.6. (1*R*,2*S*)-6,6-Dimethyl-2-[2-(2-methylbuten-2-yloxy)-ethylbicyclo[3.1.1]hept-2-ene 1f. Ether–petroleum ether (5:95), 94% yield, oil, $[\alpha]_D^{20}=-29.7$ (*c* 1, $CHCl_3$). IR (film): 3010, 1675, 1650 cm^{-1}. ^1H NMR: 0.84 (s, 3H, CH_3), 1.16 (d, 1H, *J*=8.4 Hz), 1.27 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.96–2.12 (m, 2H), 2.12–2.41 (m, 5H), 3.42 (t, 2H, *J*=7.2 Hz, C*H*OR), 3.94 (d, 2H, *J*=6.9 Hz; CH_2–CH=C), 5.26 (m, 1H, C=C*H*), 5.35 (brt, 1H, *J*=6.8 Hz, C*H*=CMe_2). ^{13}C NMR: 18.0, 21.2, 25.8, 26.4, 31.4, 31.7, 37.3, 38.0, 40.8, 45.9, 67.1, 68.6, 117.7, 121.4, 136.6, 145.3. Anal. calcd for $C_{16}H_{26}O_2$: C, 81.99, H, 11.18, O, 6.83. Found: C, 82.04, H, 11.20, O, 6.76.

4.2.7. 3-Methyl-2-butenyl 1-methylcyclohexyl ether 1g. Ether–petroleum ether (2:98), 82% yield, liquid. IR (film): 3020, 1670 cm^{-1}. ^1H NMR: 1.14 (s, 3H, CH_3), 1.19–1.63 (m, 10H, 5CH_2), 1.66 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 3.84 (d, 2H, *J*=6.75 Hz, OCH_2), 5.32 (brt, 1H, *J*=6.78 Hz, C*H*=CMe_2). ^{13}C NMR: 18.0, 22.4 (2C), 24.6, 25.8, 25.9, 36.6 (2C), 57.3, 73.4, 122.6, 135.1. Anal. calcd for $C_{12}H_{22}O$: C, 79.06, H, 12.16, O, 8.78. Found: C, 79.38, H, 12.11, O, 8.51.

4.2.8. 3-Methyl-2-butenyl 3-[4-(3-methyl-2-butenyloxy)-phenyl]propyl ether 1l. Ether–petroleum ether (1:9), 93% yield, oil. IR (film): 1670, 1610, 1580 cm^{-1}. ^1H NMR: 1.7 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 1.88 (q, 2H, *J*=6.4 Hz, CH_2–CH_2O), 2.65 (t, 2H, *J*=6.5 Hz, CH_2Ar), 3.42 (t, 2H, *J*=6.5 Hz, Ar(CH_2)$_2$CH_2O), 3.95 (d, 2H, *J*=6.9 Hz, CH_2–CH=C), 4.49 (d, 2H, *J*=6.75 Hz, CH_2OAr), 5.39 (brt, 1H, *J*=6.9 Hz, C*H*=CMe_2), 5.51 (brt, 1H, *J*=6.8 Hz, C*H*=CMe_2), 6.83 (d, 2H, *J*=8.6 Hz, Ar), 7.10 (d, 2H, *J*=8.6 Hz, Ar). ^{13}C NMR: 18.1, 18.2, 25.8 (2C), 31.5, 31.6, 64.8, 67.3, 69.4, 114.5 (2C), 120.0, 121.4, 129.3 (2C), 134.1, 136.7, 137.9, 157.1. Anal. calcd for $C_{19}H_{28}O_2$: C, 79.12, H, 9.78, O, 11.09. Found: C, 78.96, H, 9.75, O, 11.04.

4.2.9. 1-[(3-Methyl-2-butenyl)oxy]-5-(2-propenyloxy)-pentane 1h. To a solution of 1,5-butanediol monoprenyl ether[23] (0.5 g, 2.9 mmol) in 6 mL of DMF, cooled to −10°C, were successively added allyl bromide (0.38 mL, 1.5 equiv.) and NaH (60% dispersion in mineral oil, 0.14 g, 1.2 equiv.). The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Excess of NaH was destroyed with MeOH and ether and water were added. The aqueous phase was extracted once with water, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (ether–petroleum ether, 1:9) to give **1h** as a liquid (0.58 g, 94%). IR (film): 3070, 1670, 1640 cm^{-1}. ^1H NMR: 1.28–1.72 (m, 6H), 1.67 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.41 (m, 4H, CH_2OAll, CH_2OPre), 3.94 (m, 4H, 2 CH_2–CH=C), 5.15 (brd, 1H, *J*=10 Hz, CH=CH_2), 5.26 (brd, 1H, *J*=17 Hz, CH=CH_2), 5.35 (brd, 1H, *J*=6.9 Hz, C*H*=CMe_2), 5.89 (ddd, 1H, *J*=5.6, 10 and 17 Hz, C*H*=CH_2). ^{13}C NMR: 18.0, 22.9, 25.8, 29.6, 29.7, 67.3, 70.2, 70.4, 71.8, 116.6, 121.4, 135.1, 136.5. Anal. calcd for $C_{13}H_{24}O_2$: C, 73.54, H, 11.39, O, 15.07. Found: C, 73.50, H, 11.46, O, 14.97.

4.2.10. 5-(3-Methyl-2-butenyloxy)-1-pentanol acetate 1i. To a solution of 1,5-butanediol monoprenyl ether[23] (0.38 g, 2.2 mmol) in 4 mL of pyridine was added acetic anhydride (2 mL). The solution was stirred for 2 h at room temperature. After evaporation of the solution to dryness, the residue was purified by chromatography on silica gel (ether–petroleum ether, 1:4), to afford **1i** as a liquid (0.43 g, 91%). IR (film): 1740, 1670 cm^{-1}. ^1H NMR: 1.35–1.48 (m, 2H), 1.53–1.65 (m, 4H), 1.65 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.39 (t, 2H, *J*=6.4 Hz, CH_2OPre), 3.93 (d, 2H, *J*=6.9 Hz, CH_2–CH=C), 4.04 (t, 2H, *J*=6.5 Hz, CH_2OAc), 5.33 (brt, 1H, *J*=6.9 Hz, C*H*=CMe_2). ^{13}C NMR: 18.0, 21.0, 22.8, 25.8, 28.5, 29.5, 64.5, 67.3, 70.0, 121.3, 136.7, 171.1. Anal. calcd for $C_{12}H_{22}O_3$: C, 67.26, H, 10.35, O, 22.40. Found: C, 67.04, H, 10.40, O, 22.81.

4.2.11. (1,1-Dimethylethyl)dimethyl[5-(3-methyl-2-butenyloxy)pentyl]oxy silane 1j. To a solution of 1,5-butanediol monoprenyl ether[23] (0.4 g, 2.3 mmol) in 8 mL of DMF were successively added imidazole (0.35 g,

2.2 equiv.) and *t*-butyldimethylchlorosilane (0.42 g, 1.2 equiv.). After stirring for 2 h at room temperature, the solution was diluted with ether, washed twice with water, dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on silica gel (ether–petroleum ether, 5:95) to give **1j** as a liquid (0.625 g, 94%). IR (film): 1670 cm^{-1}. ^1H NMR: 0.04 (s, 6H, $SiMe_2$), 0.89 (s, 9H, Si*t*-Bu), 1.32–1.47 (m, 2H), 1.48–1.65 (m, 4H), 1.67 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 3.40 (t, 2H, *J*=6.5 Hz, CH_2OPre), 3.61 (t, 2H, *J*=6.4 Hz, CH_2OSi), 3.94 (d, 2H, *J*=6.9 Hz, CH_2–CH=C), 5.35 (brt, 1H, *J*=6.9 Hz, C*H*=CMe_2). ^{13}C NMR: 18.0, 18.4, 22.5, 24.6, 25.8, 26.0 (3C), 29.6, 32.7, 63.2, 67.3, 70.3, 121.4, 136.6. Anal. calcd for $C_{16}H_{34}O_2Si$: C, 67.07, H, 11.96. Found: C, 66.84, H, 11.90.

4.2.12. (1,1-Dimethylethyl)diphenyl[5-(3-methyl-2-butenyloxy)pentyl]oxy silane 1k. To a solution of 1,5-butanediol monoprenyl ether[23] (0.5 g, 2.9 mmol) in 10 mL of DMF were successively added imidazole (0.434 g, 2 equiv.) and *t*-butyldiphenylchlorosilane (0.9 mL, 1.2 equiv.). After stirring for 3 h at room temperature, the solution was diluted with ether, washed twice with water, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by chromatography on silica gel (ether–petroleum ether, 5:95) to give **1k** as a liquid (1.15 g, 97%). IR (film): 3120, 3060, 3040, 3010, 1670, 1590 cm^{-1}. ^1H NMR: 1.08 (s, 9H, *t*-Bu), 1.43–1.63 (m, 6H), 1.68 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 3.41 (t, 2H, *J*=6.5 Hz, CH_2OPre), 3.69 (t, 2H, *J*=6.4 Hz, CH_2OSi), 3.95 (d, 2H, *J*=6.9 Hz, CH_2–CH=C), 5.38 (brt, 1H, *J*=6.9 Hz, C*H*=CMe_2), 7.43 (m, 6H, Ar), 7.72 (m, 4H, Ar). ^{13}C NMR: 18.1, 19.3, 22.6, 25.9, 27.0 (3C), 32.5, 64.0, 67.3, 70.3, 121.6, 127.7 (4C), 129.6 (2C), 134.2 (2C), 135.6 (4C), 136.6. Anal. calcd for $C_{26}H_{38}O_2Si$: C, 76.04, H, 9.33. Found: C, 76.09, H, 9.43.

4.3. General procedure for the cleavage of prenyl ethers

Method A: iodine in dichloromethane. To a solution of 1 mmol of the prenyl ether in 10 mL of dry dichloromethane, cooled to 0°C, was added iodine (in most cases (0.381 g, 1.5 equiv.) except for **1e** and **1h** (3 equiv.) and for **1k** (2 equiv.)). In the case of acid sensitive subsrates 3 Å molecular sieves was added prior to iodine (0.1 g of 3 Å molecular sieves/0.1 g of iodine). The reaction was warmed up to room temperature and monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2, washed with saturated sodium thiosulfate solution followed by water. After drying the organic phase (Na_2SO_4), solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel.

Method B: DDQ in CH_2Cl_2–H_2O (9:1). To a stirred solution of prenyl ether (1 mmol) in 9 mL of CH_2Cl_2 was added water (1 mL) and DDQ (0.272 g, 1.2 equiv.). Reaction progress was monitored by TLC. Upon consumption of the prenyl ether, 2,3-dichloro-5,6-dicyanohydroquinone was filtered. To the filtrate, saturated $NaHCO_3$ solution was added, and the aqueous phase was extracted twice with CH_2Cl_2. Drying over Na_2SO_4, and evaporation to dryness gave a material that was purified by flash chromatography.

4.3.1. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose 2a. *Method A*. (Ether–petroleum ether, 2:1), 61% yield, crystalline solid, mp 107–110°C, $[\alpha]_D^{20}=-18$ (*c* 4.2, H_2O) (lit.[24] mp 110°C, $[\alpha]_D=-18.5$ (*c* 5, H_2O)). Spectroscopic data are in accordance with those of an authentic sample.

Method B. 65% Yield, solid, mp 110–111°C, $[\alpha]_D^{20}=-17.5$ (*c* 3, H_2O).

4.3.2. 3-*O*-Benzyl-1,2-isopropylidene-α-D-glucofuranose 2b. *Method A*. I_2, 3 equiv., (ether), 50% yield, oil, $[\alpha]_D^{20}=-50.4$ (*c* 1.6, $CHCl_3$) (lit.[22] $[\alpha]_D^{20}=-49.9$ (*c* 1.08, $CHCl_3$). ^1H NMR data were in perfect agreement with those described.[22]

Method B. DDQ, 3 equiv., 68% yield, $[\alpha]_D^{20}=-49.5$ (*c* 1, $CHCl_3$).

4.3.3. 3-*O*-Benzyl-1,2-*O*-isopropylidene-6-*O*-(3-methyl-2-butenyl)-α-D-glucofuranose 3b. *Method A*. (Ether–petroleum ether, 1:1), 54% yield, oil. It was characterized as its acetate: oil, $[\alpha]_D=-52.9$ (*c* 3.6, $CHCl_3$). IR (film): 3050, 3040, 3020, 1740, 1670 cm^{-1}. ^1H NMR: 1.33 (s, 6H, CH_3), 1.5 (s, 6H, CH_3), 1.65 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.95 (s, 3H, OAc), 3.63 (dd, 1H, *J*=4.6 and 11.4 Hz, H-6a), 3.81 (dd, 1H, *J*=2.3 and 11.4 Hz, H-6b), 3.91–4.1 (m, 3H, H-3, CH_2–CH=C), 4.43 (dd, 1H, *J*=3 and 9.5 Hz, H-4), 4.45 (d, 1H, *J*=11.5 Hz, CH_2Ph), 4.6 (d, 1H, *J*=3.75 Hz, H-2), 4.62 (d, 1H, *J*=11.6 Hz, CH_2Ph), 5.22–5.38 (m, 2H, H-5 and CH=CMe_2), 5.91 (d, 1H, *J*=3.7 Hz, H-1). ^{13}C NMR: 18.1, 21.1, 25.8, 26.4, 26.8, 67.8, 68.6, 69.9, 72.1, 77.8, 81.1, 81.8, 105.3, 112.0, 121.1, 128.0, 128.2 (2C), 128.5 (2C), 137.0, 137.1, 159.8. Anal. calcd for $C_{23}H_{32}O_7$: C, 65.7, H, 7.67, O, 26.63. Found: C, 65.69, H, 7.75, O, 26.55.

Method B. With 1 equiv. of DDQ, two products were formed. Elution with (ether–petroleum ether, 1:1) gave first **3b** (33% yield) followed by 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-(3-methyl-2-butenyl)-α-D-glucofuranose (27% yield). ^1H NMR: 1.32 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 3.7–4.02 (m, 3H, H-5, 2H-6), 4.05–4.19 (m, 3H, H-3, CH_2–CH=C), 4.24 (dd, 1H, *J*=3 and 9.5 Hz, H-4), 4.56 (d, 1H, *J*=11.5 Hz, CH_2Ph), 4.62 (d, 1H, *J*=3.8 Hz, H-2), 4.73 (d, 1H, *J*=11.5 Hz, CH_2Ph), 5.28 (brt, 1H, *J*=6.8 Hz, C*H*=CMe_2), 5.91 (d, 1H, *J*=3.8 Hz, H-1). ^{13}C NMR: 18.0, 25.8, 26.4, 26.8, 62.1, 66.6, 72.0, 75.3, 80.0, 81.8, 105.1, 112.0, 121.0, 127.6 (2C), 127.9, 128.5 (2C), 137.2, 137.5.

4.3.4. 1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose 2c. *Method A*. (Ether–petroleum ether, 2:1), 72% yield, oil, $[\alpha]_D=-57$ (*c* 1.2, $CHCl_3$) (lit.[24] $[\alpha]_D^{20}=-55$ (*c* 3.5, $CHCl_3$)). Its spectroscopic data were in accordance with those of an authentic sample.

Method B. 89% Yield, $[\alpha]_D=-54.3$ (*c* 2.5, $CHCl_3$).

4.3.5. (1*R*,2*S*,5*R*)-Menthol 2d. *Method A*. (Ether–petroleum ether, 1:3), 92% yield, solid, mp 41–43°C, $[\alpha]_D=-48.2$ (*c* 2, EtOH) (lit.[25] mp 41–43°C, $[\alpha]_D=-50$ (10% alcoholic solution)). NMR data were in accordance with those of an authentic sample.

Method B. 86% Yield, solid, mp 42–43°C, $[\alpha]_D=-50.2$ (*c* 5, EtOH).

4.3.6. Testosterone 2e. *Method A*. (Ether–petroleum ether, 4:1), 79% yield, solid: mp 150–153°C, $[\alpha]_D=+107$ (*c* 2.1, EtOH). (Lit.[25] mp 155°C, $[\alpha]_D^{24}=+109$ (*c* 4, EtOH)). NMR data were in agreement with a sample from a commercial source.

Method B. 89% Yield, solid, mp 152–155°C, $[\alpha]_D=+110$ (*c* 1.5, EtOH).

4.3.7. (−)-Nopol 2f. *Method B*. (Ether–petroleum ether, 1:2), 78% yield, oil. Physical and spectroscopic data were in agreement with those of an authentic sample.

4.3.8. 1-Methylcyclohexanol 2g. *Method A*. Purification by flash chromatography (ether–petroleum ether, 1:2) followed by distillation in a Kugelrohr apparatus gave pure 2 g (75% yield) as an oil which crystallized on standing: mp 25–26°C. Its NMR data were identical with those of a commercial sample.

Method B. 72% Yield, mp 24–26°C.

4.3.9. 5-(2-Propenyloxy)-1-pentanol 2h. *Method A*. Two products were obtained: **2h** and its corresponding *vic*-diiodo **5** purified by filtration on a pad of silica gel (ether–petroleum ether, 2:1). Treatment of the mixture (0.19 g obtained from 0.15 g of starting material **1h**) with powdered zinc (0.13 g) in 4 mL of hot ethanol (60°C) and purification by flash chromatography gave pure **2h** as a liquid (0.081 g, 80% yield). ^{1}H NMR: 1.28–1.72 (6H, m), 2.55 (s, 1H, OH), 3.39 (t, 2H, *J*=6.3 Hz, C*H*$_2$OAll), 3.58 (t, 2H, *J*=6.4 Hz, C*H*$_2$OH), 3.93 (dt, 2H, *J*=5.6 and 1.4 Hz, C*H*$_2$–CH=CH$_2$), 5.12 (brd, 1H, *J*=10 Hz, CH=C*H*$_2$), 5.22 (dq, 1H, *J*=1.5 and 17 Hz, CH=C*H*$_2$), 5.88 (ddd, 1H, *J*=5.6, 10 and 17 Hz, C*H*=CH$_2$). ^{13}C NMR: 22.4, 29.4, 32.4, 62.5, 70.3, 71.8, 116.8, 134.9. Anal. calcd for $C_8H_{16}O_2$: C, 66.63, H, 11.18. Found: C, 66.55, H, 11.22.

Method B. 86% Yield. ^{1}H and ^{13}C NMR data were identical with those of a sample obtained via method A.

4.3.10. 5-Hydroxypentylacetate 2i. *Method A*. (Ether–petroleum ether, 2:1), 77% yield, liquid. Its spectroscopic data were in perfect agreement with those described in the literature.[26]

Method B. 94% Yield.

4.3.11. 5-*t*-Butyldimethylsilyloxypentan-1-ol 2j. *Method A*. (Ether–petroleum ether, 2:1), 22% yield, oil. Its spectroscopic data were in accordance with those reported in the literature.[27]

Method B. **2j** was separated from 3-methyl-1-butenal by flash chromatography (ether–petroleum ether, 2:1), 80% yield.

4.3.12. 5-*t*-Butyldiphenylsilyloxypentan-1-ol 2k. *Method A*. (Ether–petroleum ether, 1:1), 70% yield, oil. Its spectroscopic data were identical with those described in the literature.[28]

Method B. 83% Yield.

4.3.13. 3-[4-(3-Methyl-2-butenyl)phenyl]-1-propanol 2l. This compound was obtained, by method B, in pure form in 36% yield, after purification on silica gel (ether–petroleum ether, 1:2). Its physical data were in agreement with those described in the literature.[29]

4.3.14. 6-(3-Hydroxypropyl)-3,4-dihydro-2,2-dimethyl-3-iodo-2*H*-1-benzopyran 4. To a solution of the diprenyl ether **1l** (0.15 g, 0.52 mmol) in 6 mL of CH_2Cl_2, cooled to 0°C, was added iodine (0.198 g, 1.5 equiv.). The reaction mixture was stirred for 90 min at 0°C and 30 min at room temperature. The brownish solution was diluted with CH_2Cl_2, washed with a saturated $Na_2S_2O_3$ solution then water. The organic phase was dried (Na_2SO_4) and evaporated to dryness. Flash chromatography of the residue (ether–petroleum ether, 1:1) gave **4** as an oil which crystallized on standing (0.102 g, 56% yield), mp 65–68°C. ^{1}H NMR: 1.48 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.9 (m, 2H, C*H*$_2$–CH$_2$OH), 2.62 (t, 2H, *J*=7.3 Hz, C*H*$_2$–CH$_2$–CH$_2$OH), 3.43 (d, 1H, *J*=8.5 Hz, C*Ha*–CHI), 3.44 (d, 1H, *J*=6.3 Hz, C*Hb*–CHI), 3.68 (t, 2H, *J*=6.4 Hz, C*H*$_2$OH), 4.42 (dd, 1H, *J*=6.5 and 8.3 Hz, CHI), 6.72 (d, 1H, *J*=8.3 Hz, Ar), 6.83 (d, 1H, *J*=1.7 Hz, Ar), 6.97 (dd, 1H, *J*=2.1 and 8.3 Hz). ^{13}C NMR: 23.5, 27.8, 31.2, 32.8, 34.4, 36.9, 62.3, 76.5, 117.4, 120.3, 128.2, 133.8, 151.1. Anal. calcd for $C_{14}H_{19}O_2$: C, 48.57, H, 5.53, O, 9.24. Found: C. 48.64, H, 5.61, O, 9.15.

4.4. Procedure for cleavage of the prenyl ether 1d using catalytic amount of I_2 or DDQ

4.4.1. With iodine. To a solution of prenyl ether **1d** (0.15 g, 0.67 mmol) in 5 mL of dry CH_2Cl_2, cooled to 0°C, was added iodine 0.068 g, 4 mol%. The reaction mixture was allowed to warm up to room temperature and stirred for 4 h 30. After an usual work-up, purification of the residue on silica gel (ether–petroleum ether, 1:3) afforded menthol **2d** as a crystalline solid (0.093 g, 89% yield).

4.4.2. With DDQ. To a solution of prenyl ether **1d** (0.15 g, 0.67 mmol) in 5 mL of CH_2Cl_2, were successively added DDQ (0.015 g, 0.1 equiv.) and $Mn(OAc)_3{\cdot}2H_2O$ (0.54 g, 3 equiv.). After stirring the brown suspension for 19 h, the salt was filtered and washed once with CH_2Cl_2. The combined organic phases were washed with a saturated $NaHCO_3$ solution and water. Drying (Na_2SO_4) the organic phase and evaporation under reduced pressure gave a residue purified on silica gel (ether–petroleum ether, 1:3). Menthol **2d** was obtained as a crystalline solid (0.087 g, 84% yield).

4.4.3. Reaction of iodine (0.4 equiv.) with the prenyl ether 1l: isolation of the intermediates. To a solution of **1l** (0.2 g, 6.94 mmol) in 6 mL of CH_2Cl_2, cooled to 0°C, was added iodine (0.071 g, 0.4 equiv.).The reaction was allowed to warm up to room temperature and stirred for 2 h. After an usual work-up, the residue was purified by flash chromatography on silica gel. Elution with ether–petroleum ether (1:2) gave 4-[3-methyl-2-butenyl)oxy]propylphenol **7** as an oil (0.04 g, 26%). ^{1}H NMR: 1.68 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 1.88 (m, 2H, C*H*$_2$–CH$_2$OPre), 2.63 (t, 2H, *J*=6.5 Hz, C*H*$_2$Ar), 3.46 (t, 2H, *J*=6.5 Hz, C*H*$_2$OPre), 3.99 (d, 2H,

J=6.9 Hz, CH_2–CH=C), 5.39 (brt, 1H, J=6.9 Hz, CH=CMe$_2$), 5.87 (s, 1H, OH), 6.75 (d, 2H, J=8.5 Hz, Ar), 7.03 (d, 2H, J=8.5 Hz, Ar). ^{13}C NMR: 18.1, 25.8, 31.49, 31.52, 67.3, 69.4, 115.3 (2C), 121.0, 129.5 (2C), 133.8, 137.2, 153.9. Anal. calcd for $C_{14}H_{20}O_2$: C, 76.33, H, 9.15. Found: C, 76.10, H, 9.21. Pursuing the elution with ether–petroleum ether (1:1) gave first compounds **2l** and the iodo **4** (ratio 7:3) as an unseparable mixture (0.018 g) and then zanthoxylol 6 (0.03 g, 2%).

4.4.4. Formation of the iodo 4 from phenol 7. To a solution of **7** (0.04 g, 0.18 mmol) in 2 mL of CH_2Cl_2 was added iodine (0.046 g, 1 equiv.). The reaction mixture was stirred for 1 h at room temperature and worked-up as usual. Chromatography of the residue on silica gel (ether–petroleum ether, 1:1) afforded **4** as a yellow oil (0.025 g, 40%).

4.4.5. 3-[4-Hydroxy-3-(3-methyl-2-butenyl)phenyl]-1-propanol 6 (zanthoxylol). To a solution of the iodo **4** (0.056 g, 0.16 mmol) in 2 mL of ethanol was added powdered zinc (0.02 g, 2 equiv.). The suspension was refluxed for 1 h, cooled down and evaporated to dryness. The residue was chromatographed on silica gel to give **6** as an oil (0.031 g, 88% yield). IR (film): 3340, 1660 cm^{-1}. ^{1}H NMR: 1.62 (brs, 1H, CH$_2$OH), 1.78 (s, 6H, 2 CH$_3$), 1.87 (m, 1H, CH_2–CH$_2$OH), 2.62 (t, 2H, J=7.2 Hz, CH_2–CH$_2$–CH$_2$OH), 3.34 (d, 2H, J=7.1 Hz, CH_2–CH=CMe$_2$), 3.69 (t, 2H, J=6.5 Hz, CH_2OH), 5.33 (brt, 1H, J=7.1 Hz, CH=CMe$_2$), 5.48 (s, 1H, OH), 6.72 (d, 1H, J=8.3 Hz, Ar), 6.92 (d, 1H, J=8.3 Hz, Ar), 6.94 (brs, 1H, Ar).[10c] ^{13}C NMR: 17.9, 25.8, 29.7, 31.3, 34.5, 62.5, 115.6, 122.1, 127.0, 127.2, 129.9, 133.8, 134.3, 152.5.

4.4.6. Synthesis of 6-(2-hydroxyethyl)-2,2-dimethyl-2*H*-1-benzopyran 10 from 8. Diprenyl ether of 2-(4-hydroxyphenyl)ethanol, compound **8**, was prepared according to the procedure described for **1l** in 95% yield. ^{1}H NMR: 1.68 (s, 3H, CH$_3$), 1.76 (s, 6H, CH$_3$), 1.81 (s, 3H, CH$_3$), 2.86 (t, 2H, J=7.4 Hz, CH_2–CH$_2$OPre), 3.61 (t, 2H, J=7.4 Hz, CH_2OPre), 3.99 (d, 2H, J=6.9 Hz, CH_2–CH=C), 4.50 (d, 2H, J=6.7 Hz, PhOCH_2–CH=C), 5.37 (brt, 1H, J=6.9 Hz, CH=CMe$_2$), 5.51 (brt, 1H, J=6.7 Hz, CH=CMe$_2$), 6.86 (d, 2H, J=8.6 Hz, Ar), 7.15 (d, 2H, J=8.6 Hz, Ar). Transformation of **8** to **9**, in the presence of iodine, was affected according to the same procedure described for **4** (oil, 55% yield). ^{1}H NMR: 1.48 (s, 3H, CH$_3$), 1.56 (s, 3H, CH$_3$), 2.77 (t, 2H, J=6.6 Hz, CH_2–CH$_2$OH), 3.43 (d, 1H, J=8.4 Hz, CHa–CHI), 3.44 (d, 1H, J=6.5 Hz, CHb–CHI), 3.80 (t, 2H, J=6.6 Hz, CH_2OH), 4.40 (dd, 1H, J=6.4 and 8.3 Hz, CHI), 6.75 (d, 1H, J=8.3 Hz, Ar), 6.86 (brd, 1H, Ar), 7.0 (dd, 1H, J=1.9 and 8.3 Hz). ^{13}C NMR: 23.8, 27.7, 32.6, 36.8, 38.3, 63.9, 76.5, 117.6, 120.5, 128.6, 129.0, 130.4, 151.5. The dehydroiodination of **9** was effected by heating a solution of **10** (0.1 g, 0.3 mmol), in 2 mL of toluene at 80°C for 4 h in the presence of **4** drops of DBU. The precipitate formed was filtered and the filtrate was washed with 1N HCl solution, water, a saturated $NaHCO_3$ solution, water again. The organic phase was dried (Na_2SO_4), evaporated to dryness and the residue was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 99:1) to give **10** as a yellow oil 0.057 g, 93% yield). ^{1}H NMR: 1.33 (s, 1H, OH), 1.43 (s, 6H, 2CH$_3$), 2.76 (t, 2H, J=6.57 Hz, CH_2–CH$_2$OH), 3.80 (t, 2H, J=6.55 Hz, CH_2OH), 5.64 (d, 1H, J=9.78 Hz, CH=CH-Ar), 6.30 (d, 1H, J=9.80 Hz, CH=CH-Ar), 6.72 (d, 1H, J=8.2 Hz, Ar), 6.84 (1H, J=2.1 Hz, Ar), 6.96 (dd, 1H, J=2.1 and 8.1 Hz, Ar). ^{13}C NMR: 28.0 (2C), 38.4, 63.8, 76.2, 116.4, 121.3, 122.3, 126.8, 129.5, 130.6, 131.0, 151.6.[14]

4.4.7. 1-Iodo-5-iodomethyl-2,2,4-trimethyl-4-cyclohexene 11 from 1d. Prenyl ether cleavage of **1d** was effected on 0.45 g (2 mmol). After an usual work-up, the residue was purified by chromatography on silica gel, eluant petroleum ether, to give **11** as a yellow oil (0.06 g, 7%). ^{1}H NMR: 0.99 (s, 3H, CH$_3$), 1.04 (s, 3H, CH$_3$), 1.58 (s, 3H, CH$_3$), 1.92 (d, 1H, J=18.5 Hz, CHa–CH(CH$_3$)$_2$), 2.04 (d, 1H, J=18.5 Hz, CHb–CH(CH$_3$)$_2$), 2.94 (m, 2H, CH_2–CHI), 3.86 (d, 1H, J=9.2 Hz, CHaI), 3.92 (d, 1H, J=9.2 Hz, CHbI), 4.33 (dd, 1H, J=6 and 8.3 Hz, CHI). ^{13}C NMR: 8.0, 18.2, 25.2, 30.0, 35.1, 40.1, 44.3, 44.5, 126.3, 132.3.

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