Catalytic, tunable, one-step bismuth(III) triflate reaction with alcohols: dehydration vs dimerization

Laura E. Kolsi, † Jari Yli-Kauhaluoma † and Vânia M. Moreira †, ‡, * †

† Drug Research Program, Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, Viikinkaari 5 E (P.O. Box 56), FI-00014, Helsinki, Finland
‡ Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, UK
**ABSTRACT:** Bi(OTf)$_3$ xH$_2$O is a powerful catalyst for the dehydration of tertiary alcohols into alkenes, in apolar solvents. The reaction proceeds smoothly and selectively, with amounts as low as 0.01 mol% catalyst, in yields up to 93%. Moreover, in polar solvents, Bi(OTf)$_3$ xH$_2$O (0.1–1 mol%) selectively catalyzes the dimerization of the alcohols instead, forming new C-C bonds, in yields up to 96%. This mild, efficient, economic and eco-friendly method is applicable across different chemical classes and amenable to several functional groups.
INTRODUCTION

The dehydration of alcohols into the corresponding alkenes is a widely used reaction in organic syntheses.\textsuperscript{1} Moreover, alkenes produced from alcohols largely present in biomass are critical raw materials for the production of plastics, fibers and polymeric products.\textsuperscript{2,3} The dehydration of alcohols into alkenes is typically made using acid catalysis at elevated temperatures.\textsuperscript{1,3} However, these reaction conditions promote side-reactions, including cyclization and rearrangement of the starting materials, and are far from ideal for compounds bearing labile chemical groups. Therefore, the pursuit of selective methods to dehydrate alcohols, through mild, cost-effective and efficient catalysis, remains a subject of interest for organic chemists.\textsuperscript{4}

Bismuth(III) salts are versatile reagents for a variety of organic reactions,\textsuperscript{5} including syntheses of pharmaceutically interesting compounds as well as natural products.\textsuperscript{6} In addition to their broad reactivity, these compounds are relatively non-toxic and easy to handle, and therefore bismuth(III)-based chemistry is viewed as eco-friendly. Within bismuth(III) salts, Bi(OTf)\textsubscript{3} xH\textsubscript{2}O is appealing because it is commercially available, inexpensive, potentially reusable and chemically versatile, as it can promote either Lewis or Brønsted acid catalysis.\textsuperscript{5h, 7}

Bismuth(III) halides react with alcohols when used in stoichiometric amounts, in carbon tetrachloride, at reflux.\textsuperscript{8} BiCl\textsubscript{3} halogenates all alcohol types other than primary, with dehydration as a side reaction to give alkenes, in low yields. Under the same conditions, BiBr\textsubscript{3} dehydrates secondary and tertiary alcohols to the corresponding alkenes but its reaction with benzylic alcohols gives ethers as the main products. Alkenes are also obtained from the reaction of secondary and tertiary alcohols with Ph\textsubscript{3}BiBr\textsubscript{2}/I\textsubscript{2}, in cyclohexane.\textsuperscript{9} However, under these conditions, some reactions are plagued by competing iodination. Altogether, these results suggest that Bi(OTf)\textsubscript{3} xH\textsubscript{2}O may be a suitable reagent for the dehydration of alcohols. Nonetheless, to the best of our knowledge no study has yet addressed this question.
As part of our ongoing work towards the semisynthesis of diterpenoids scarcely available from their natural sources, we recently became interested in suitable methods to build a 13-propenyl side chain onto the diterpenic alcohol 1. This modification is common to antiochic acid, diterpenoids from *Pinus massoniana*, aquilarabietic acid H from Chinese eaglewood and bodinieric acids C and F from *Callicarpa bodinieri*, some bearing relevant bioactivities. However, literature searches revealed that the methods available require halogenated reagents, non-green solvents or metals in strong acidic solutions, which are difficult to integrate in total syntheses campaigns. Therefore, we first studied the reactivity of Bi(OTf)$_3$·xH$_2$O towards alcohol dehydration using 1 as a starting material.

**RESULTS AND DISCUSSION**

In the presence of 5 mol% Bi(OTf)$_3$·xH$_2$O, in refluxing chloroform, 1 was successfully converted into 2, after 2 hours and in 63% yield, after chromatographic purification (Table 1, Entry 1). Similar results were observed with 1 mol% of Bi(OTf)$_3$·xH$_2$O (Entry 2) and the overall the amount of salt could be lowered to 0.1 mol%, with gain in yield and extension of the reaction time (Entry 3). However, under these reaction conditions, formation of 3 as a side product, with an ethoxy group at position 15 occurred (Scheme 1), most likely due to the presence of ethanol used as a stabilizer for chloroform.

**TABLE 1. Catalytic Bi(OTf)$_3$·xH$_2$O-mediated dehydration of 1.**

![Chemical structures](image-url)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Productb</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>CHCl₃</td>
<td>2</td>
<td>63</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>CHCl₃</td>
<td>2</td>
<td>74</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>CHCl₃</td>
<td>24</td>
<td>85</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>CH₂Cl₂</td>
<td>2</td>
<td>88</td>
<td>0</td>
<td>traces</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>0.1</td>
<td>CH₂Cl₂</td>
<td>24</td>
<td>84</td>
<td>0</td>
<td>traces</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>EtOHd</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>EtOHd</td>
<td>24</td>
<td>4</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>EtOHd</td>
<td>24</td>
<td>23</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>EtOHd</td>
<td>24</td>
<td>7</td>
<td>73</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>20</td>
<td>EtOHd</td>
<td>2</td>
<td>8</td>
<td>74</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>EtOH</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>38e</td>
<td>43e</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0.1</td>
<td>1,4-dioxaned</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>74</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>THF</td>
<td>24</td>
<td>90</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>CH₃CN</td>
<td>2</td>
<td>47</td>
<td>0</td>
<td>57</td>
<td>traces</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>10</td>
<td>CH₃CN</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td>55e</td>
<td>23e</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>0.1</td>
<td>CH₂NO₂</td>
<td>24</td>
<td>23</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>CH₂NO₂</td>
<td>2</td>
<td>18</td>
<td>0</td>
<td>71</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

aGeneral experimental conditions: compound 1 (0.050 g, 0.15 mmol), solvent (1.8 mL), reflux;
bYield after purification by FCC; cReaction made at room temperature; dDry solvent; eYield calculated from the ¹H NMR spectra.

To rule out this effect, we next screened the reaction in dichloromethane (Table 1, Entries 4-5) and in ethanol (Entries 6-11). Indeed, in dichloromethane, the reaction proceeded with 0.1 mol% of Bi(OTf)₃ xH₂O, at reflux or room temperature, without formation of 3 and the alkene 2 was isolated, in 84-88% yield. The reaction was slower at room temperature and a small amount of 1 remained unmodified. In addition, traces of a side product which we later identified as dimeric compound 4 formed (Entries 4-5). No reactivity was observed in dry ethanol with 0.1 mol% of Bi(OTf)₃ xH₂O (Entry 6) and when the amount of salt was increased to 20 mol% increasing amounts of 3 formed as expected (Entries 7-10). However, in non-dry ethanol (Entry 11), a major change in the reactivity occurred. Compound 3 did not form and a mixture of the
two dimeric compounds 4 and 5 was instead obtained. This result pointed to the dramatic effect of water in the reaction outcome.

The results in dry 1,4-dioxane (Entries 12-13) corroborated this finding and further revealed that solvent polarity is another crucial parameter towards the reaction outcome. Thus, there was no reactivity with 0.1 mol% of Bi(OTf)$_3$ xH$_2$O in dry solvent, at reflux, whereas 74% of 2 was isolated as the single reaction product, using 1 mol% of salt, under the same conditions. In the absence of water 4 and 5 did not form and in non-polar solvents such as 1,4-dioxane and dichloromethane the formation of the alkene derivative 2 was favored. A very high yield of 2 was also obtained in relatively non-polar THF (Entry 14), even if non-dry. In polar, non-dry solvents such as acetonitrile or nitromethane (Entries 15-18), in a similar fashion to ethanol (Entry 11), 4 and 5 became the major reaction products. The use of 1 mol% of Bi(OTf)$_3$ xH$_2$O in refluxing nitromethane was ideal for the preparation of 4.

The findings in Table 1 suggest a Brønsted acid behavior for Bi(OTf)$_3$ xH$_2$O as opposed to Lewis acid, in the reaction mechanism, i.e., triflic acid is produced in situ from Bi(OTf)$_3$ xH$_2$O, which then drives the reaction forward (Scheme 1). To gain further evidence of Brønsted acid-mediated catalysis, 1 was reacted with Bi(OTf)$_3$ xH$_2$O (1 mol%), in dichloromethane, at reflux, in the presence of 2,6-di-t-butylpyridine (10 mol%), a proton scavenger that is unable to coordinate to metal ions due to the bulky t-butyl groups. No reactivity was observed indicating the need for protons in the reaction medium to promote it, according to Scheme 1. In addition,

---

1 The configuration of dimeric compound 5 was assigned to $E$ based on the NOESY correlation between the 17'$'$-H signal of the double bond at 6.14 ppm and the methyl group protons signals at 1.51 ppm (Table 1).

6
when the reaction was made using triflic acid (10 mol%), full conversion of 1 into 2, 4 and 5 occurred in 58%, 25%, 6% yields, respectively, in 2 hours.

We also investigated whether Bi(OTf)₃ xH₂O could promote the direct homodimerization of 2 based on a previous study on the heterodimerization of vinylarenes where indium triflate was a Lewis acid catalyst. However, we found that this was not the case as in refluxing 1,4-dioxane, with 5 mol% of Bi(OTf)₃ xH₂O, no reactivity was observed and with 10 mol%, formation of a mixture of dimers 4 and 5 occurred, without exhaustion of the starting material. Exploration of other solvents including a 3:1 mixture of THF and cyclohexane in the presence of 10 mol% of Bi(OTf)₃ xH₂O resulted in no reactivity, even after 24 hours, at reflux. Nitromethane was the best solvent for this modification, however 5 mol% of Bi(OTf)₃ xH₂O were required, and several products formed among which the mixture of dimers 4 and 5 was the major.

Overall, the results suggest that the alkene 2 is formed by protonation of the hydroxy group at position C13 of 1, which forms a good leaving group and a very stable tertiary carbocation (Scheme 1). Compound 3 forms in chloroform only due to the presence of ethanol which acts as a nucleophile. Dimers 4 and 5 form after electrophilic addition of the carbocation to the double bond of 2. A new tertiary carbocation forms which is converted into 4 and 5 in the presence of water. In non-dry solvents, water originates most likely from Bi(OTf)₃ xH₂O which is hygroscopic. Of note, the formation of 4 and 5 is in line with previous reports describing the dimerization of styrene catalyzed by acids as well as via proton transfer to carbonyl compounds. The “super acid” triflimide was also reported to promote the hydroalkenylation of vinylarenes. In all cases, the formation of a benzylic cation which suffers attack by vinylarenes through nucleophilic addition, followed by deprotonation to form the dimeric product is proposed as the reaction mechanism.
SCHEME 1. Proposed reaction mechanism

Different metal salts were next screened for comparison with Bi(OTf)$_3$ xH$_2$O. The results are depicted on Table 2, showing that none of the tested salts was better for the synthesis of 2 from 1.

**TABLE 2. Catalyst screening for the dehydration of 1.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Time (h)</th>
<th>Product$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>BiCl$_3$ (5)</td>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>BiCl$_3$ (10)</td>
<td>24</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>BiBr$_3$ (10)</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OTf)$_2$. (5)</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OTf)$_2$. (7.5)</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>Sc(OTf)$_3$. (5)</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>Sc(OTf)$_3$. (15)</td>
<td>24</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>Yb(OTf)$_3$. (20)</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>La(OTf)$_3$. (20)</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td>In(OTf)$_3$. (10)</td>
<td>2</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>In(OTf)$_3$. (20)</td>
<td>2</td>
<td>47</td>
</tr>
</tbody>
</table>

$^a$General experimental conditions: Compound 1 (0.050 g, 0.15 mmol), CH$_2$Cl$_2$ (1.8 mL), reflux.

$^b$Yield after purification by FCC.
We further investigated the scope of the reaction using other diterpenic benzylic alcohols (6-9), bearing different functional groups (Scheme 2). We extended the set to accommodate the non-benzylic terpenic tertiary alcohol cedrol 14, the non-terpenic benzylic alcohol 16, a non-benzylic tertiary alcohol 19, as well as the steroidal secondary alcohol 5α-cholestan-3β-ol 22.

The reaction was successful in all diterpenic alcohols tested although there was a need to increase the amounts of catalyst used in order to exhaust the starting materials, most likely due to the presence of atoms which coordinate with Bi(OTf)₃·xH₂O and somewhat diminish its catalytic power. Nonetheless, compounds 10-13 were all successfully prepared and isolated in yields ranging from 63 to 83%, after chromatographic purification. The reaction was also successful for the dehydration of cedrol 14 into cedrene 15, in 91% yield.

**SCHEME 2. Scope of the reaction.** Yields after purification by FCC. a5 mol% Bi(OTf)₃·xH₂O was used. bDetermined by gas chromatography-mass spectrometry (GC-MS). cCalculated from the ¹H-NMR spectrum.
Notably, alcohol 16 gave the alkene 17 and the dimer 18, with 94.6% conversion, in an 83:17 ratio, with as little as 0.01 mol% of catalyst. Moreover, alcohol 19 gave alkenes 20 and 21 in a ratio of 93:7, with a 96.6% conversion, albeit with a higher amount of catalyst, reflecting the lower reactivity of non-benzylic alcohols towards this method. In line with this finding, the reaction was unsuccessful for the dehydration of 22. These results support the proposed reaction mechanism which proceeds via formation of a carbocation and the observed reactivity reflects the stability of the participant carbocation formed in each case, i.e., benzylic alcohols are the most reactive followed by tertiary alcohols and secondary alcohols are unreactive.
In nitromethane, alcohol 16 gave the indane derivative 23 with an amount as low as 0.1 mol% catalyst, in 67% yield, along with the dimeric products 24 and 18 as minor products (Scheme 2). This result is not entirely surprising as a previous study reports the preparation of 23 from 16 in the presence of stoichiometric amounts of BiBr₃ in chloroform, after cyclization of 18, at high temperature. In sharp contrast, using an amount as low as 0.1 mol% of Bi(OTf)₃ xH₂O in nitromethane, we prepared the dimer 18 from the small alcohol 16, as the single reaction product, at room temperature, in 96% yield. Cyclization towards indane products was never observed with 1 most likely due to stereochemical impediment.

To illustrate the utility of our method, we used Bi(OTf)₃ xH₂O as an alcohol dehydrating agent for the unprecedented semisynthesis of diterpenoids from Pinus massoniana, starting from commercially available dehydroabietic acid 25 (Scheme 3). The alkene 2 was a key intermediate and the desired product 27 was synthesized over 5 steps.

SCHEME 3. Semisynthesis of 13-propenyl-7-hydroxyabieta-8,11,13-trien-18-oic acid 27

The α-orientation of H-7 was assigned by the presence of a NOESY-correlation of H-5/H-7 and the broad triplet at 4.75 (t, J = 8.8 Hz), consistent with a previous study (see reference 12).
In conclusion, herein we show that the reaction of Bi(OTf)$_3$ xH$_2$O with tertiary alcohols is tunable towards obtaining either alkenes or dimers, in high yields and selectivity. This method employs an eco-friendly and relatively inexpensive catalyst, in very low loading, for accessing two different, novel and practical synthetic methodologies, under reaction conditions amenable to a variety of functional groups. We believe this method is of general utility in the field of organic chemistry and can in addition be easily incorporated into total syntheses design.
EXPERIMENTAL

General Remarks. Dehydroabietic acid (90% purity) was purchased from Pfaltz & Bauer, USA and other reagents were obtained from Sigma Aldrich Co, VWR International Oy or Fluorochem Ltd. Silica gel 60 F254 was used for thin layer chromatography (TLC). Flash column chromatography (FCC) was made with a Biotage High-Performance Flash Chromatography Sp4-system (Uppsala, Sweden). The apparatus has a 0.1-mm path length flow cell UV detector/recorder module (fixed wavelength: 254 nm). SNAP cartridges of 10 g, 25 g or 50 g were used in the purifications with a flow rate of 10–50 mL/min. A Vertex 70 (Bruker Optics Inc., MA, USA) FTIR instrument was used to collect the IR spectra, with a horizontal attenuated total reflectance (ATR) accessory (MIRacle, Pike Technology, Inc, WI, USA). Transmittance (4000 to 600 cm⁻¹) was recorded at a 4 cm⁻¹ resolution and spectra were produced with the OPUS 5.5 (Bruker Optics Inc., MA, USA) software. For NMR analysis collected on a Bruker Ascend 400 spectrometer, in CDCl₃ or MeOD with tetramethylsilane (TMS) as the internal standard, chemical shifts are reported in parts per million (ppm) and on the δ scale from TMS. The coupling constants J are quoted in Hertz (Hz). A Waters UPLC-ESI/QTOF-MS using a Synapt G2 HDMS (Waters, MA, USA) instrument was used for exact mass analysis. Purity was executed with Waters Acquity® UPLC system (Waters, Milford MA, USA) attached to Acquity PDA detector and Waters Synapt G2 HDMS mass spectrometer (Waters, Milford MA, USA) via an ESI ion source. An Agilent 7890A GC system attached to Agilent 7000 GS/MS Triple Quad was used for collection of GC-MS. The preparation and characterization of compounds 6, 8 and 9 has been previously reported.¹⁰ Compounds 3, 4, 10, 11, 12 and 13 have not been previously reported and were obtained as amorphous solids.
General procedure for the Bi(OTf)$_3$ xH$_2$O catalyzed dehydration of alcohols. To a stirred solution of the alcohol (0.050 g) in dichloromethane (1.8 mL) Bi(OTf)$_3$ xH$_2$O was added. The temperature was raised to reflux and stirring was continued for 2 hours. The solvent was evaporated under vacuum, the residue was diluted with ethyl acetate (10 mL), and water (5 mL) was added. The aqueous phase was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of NaHCO$_3$ (10 mL), water (10 mL), brine (10 mL), dried over anhydrous Na$_2$SO$_4$, and filtered. After removal of the solvent under reduced pressure, the resulting crude product was purified by flash chromatography on silica gel using ethyl acetate in n-hexane (0→100%) as the eluent.

13-Propenyl-7-oxoabieta-8,11,13-trien-18-oate (2): white solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.27 (s, 3H), 1.34 (s, 3H), 1.74 (m, 5H), 2.15 (m, 3H), 2.36 (m, 2H), 2.72 (m, 2H), 3.65 (s, 3H), 5.11 (m, 1H), 5.41 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.65 (dd, $J = 8.3$, 2.2 Hz, 1H), 8.08 (d, $J = 2.2$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 16.5, 18.3, 21.8, 23.8, 36.7, 37.2, 37.6, 38.0, 43.9, 46.8, 52.4, 113.2, 123.6, 124.4, 130.7, 131.3, 139.4, 142.2, 154.5, 177.9, 198.5. IR (ATR) 2947, 2928, 1724, 1676, 1250, 1124, 895, 841 cm$^{-1}$. HRMS $m/z$: calcd. for C$_{21}$H$_{27}$O$_3$ 327.1961 [M+H]$^+$, found 327.1960.

15-Ethoxy-7-oxoabieta-8,11,13-trien-18-oate (3): pale semi-solid. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.16 (t, $J = 7.0$ Hz, 3H), 1.27 (d, $J = 0.8$ Hz, 3H), 1.35 (s, 3H), 1.53 (s, 3H), 1.54 (s, 3H), 1.76 (m, 5H), 2.36 (m, 2H), 2.73 (m, 2H), 3.20 (q, $J = 7.0$ Hz, 2H), 3.66 (s, 3H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.66 (dd, $J = 8.3$, 2.2 Hz, 1H), 7.98 (d, $J = 2.2$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 16.0, 16.5, 18.3, 23.8, 28.4, 28.5, 36.7, 37.2, 37.5, 38.0, 43.9, 46.9, 52.4, 58.3, 76.4, 123.7, 124.5, 130.6, 131.9, 145.3, 154.1, 178.0, 198.5. IR 2978, 1726, 1682, 1236, 1069, 756 (ATR) cm$^{-1}$. HRMS $m/z$: calcd. for C$_{23}$H$_{33}$O$_4$ 373.2379 [M+H]$^+$, found 373.2380.
**Dimeric compound (4):** white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.20 (m, 3H), 1.23 (s, 3H), 1.25 (d, $J = 3.4$ Hz, 6H), 1.34 (d, $J = 1.7$ Hz, 6H), 1.70 (m, 10H), 2.33 (m, 4H), 2.69 (m, 4H), 2.84 (s, 2H), 3.67 (s, 3H), 3.76 (s, 3H), 4.85 (d, $J = 1.5$ Hz, 1H), 5.18 (d, $J = 1.5$ Hz, 1H), 7.16 (m, 2H), 7.33 (dd, $J = 8.2$, 2.2 Hz, 1H), 7.41 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.88 (d, $J = 2.1$ Hz, 1H), 7.93 (d, $J = 2.3$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 16.5, 18.3, 23.9, 23.9, 28.9, 36.6, 36.6, 37.1, 37.3, 37.5, 38.0, 38.6, 43.9, 44.0, 46.8, 49.1, 52.4, 52.4, 118.1, 123.0, 123.3, 124.8, 125.2, 130.2, 130.5, 132.3, 132.3, 141.4, 145.3, 147.4, 152.7, 154.0, 177.9, 178.0, 198.4, 198.6. IR (ATR) 2943, 1724, 1682, 1244, 1111, 754 cm$^{-1}$. HRMS m/z: calcd. for C$_{42}$H$_{53}$O$_6$ 653.3842 [M+H]$^+$, found 653.3843.

**Methyl 15-propenyl-7-oxo-N-(abieta-8,11,13-trien-18-oyl) glycinate (10).** Using the general procedure, compound 10 was prepared from 6.$^9$ Compound 10: white solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.27 (s, 3H), 1.40 (s, 3H), 1.68 (m, 2H), 1.86 (m, 3H), 2.15 (m, 3H), 2.37 (m, 1H), 2.46 (m, 1H), 2.69 (m, 2H), 3.77 (s, 3H), 4.03 (dd, $J = 5.0$, 1.7 Hz, 2H), 5.10 (m, 1H), 5.40 (m, 1H), 6.32 (m, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.65 (dd, $J = 8.3$, 2.2 Hz, 1H), 8.05 (d, $J = 2.2$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 16.5, 18.4, 21.8, 23.8, 36.9, 37.1, 37.4, 37.6, 41.8, 44.0, 46.6, 52.6, 113.1, 123.5, 124.4, 130.8, 131.2, 139.4, 142.2, 154.5, 170.6, 177.4, 198.4. IR (ATR) 3362, 2939, 1745, 1643, 1244, 1111, 891, 839 cm$^{-1}$. HRMS m/z: calcd. for C$_{23}$H$_{30}$NO$_4$ 384.2175 [M+H]$^+$, found 384.2176.

**13-Propenyl-7-oxoabieta-8,11,13-trien-18-oic acid (11).** Using the general procedure, compound 11 was prepared from 7. Compound 11: yellowish solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.28 (s, 3H), 1.36 (s, 3H), 1.66 (m, 1H), 1.83 (m, 3H), 2.15 (m, 3H), 2.37 (m, 1H), 2.53 (m, 1H), 2.75 (m, 2H), 5.11 (m, 1H), 5.41 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 1H), 7.66 (dd, $J = 8.3$, 2.2 Hz, 1H), 8.09 (d, $J = 2.2$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 16.3, 18.2, 21.8, 23.7, 36.6, 37.1, 37.5, 37.9, 43.6, 46.5, 113.2, 123.7, 124.5, 130.7, 131.4, 139.5, 142.2, 154.5,
183.0, 198.7. IR (ATR) 3256, 2943, 1722, 1668, 1248, 1165, 897, 791 cm⁻¹. HRMS m/z: calcd. for C₂₀H₂₅O₃ 313.1804 [M+H]⁺, found 313.1803.

**Dimethyl 13-isopropenyl-7-oxoabieta-8,11,13-trien-18-amide (12).** Using the general procedure, compound 12 was prepared from 8.¹⁰ Compound 12: white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.28 (s, 3H), 1.44 (s, 3H), 1.62 (m, 1H), 1.78 (m, 3H), 1.92 (m, 1H), 2.16 (m, 3H), 2.34 (m, 1H), 2.64 (m, 2H), 2.96 (t, J = 8.6 Hz, 1H), 3.02 (s, 6H), 5.10 (m, 1H), 5.41 (m, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.64 (dd, J = 8.3, 2.2 Hz, 1H), 8.07 (d, J = 2.2 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 18.5, 18.7, 21.8, 24.0, 35.6, 36.9, 37.8, 38.4, 39.2, 43.9, 45.8, 112.9, 123.3, 124.2, 130.9, 131.0, 139.2, 142.2, 154.7, 176.9, 199.2. IR (ATR) 2945, 1676, 1618, 1240, 893, 849 cm⁻¹. HRMS m/z: calcd. for C₂₂H₃₀NO₂ 340.2277 [M+H]⁺, found 340.2279.

**13-Propenyl-7-oxoabieta-8,11,13-trien-18-amide (13).** Using the general procedure, compound 13 was prepared from 9.¹⁰ Compound 13: white solid. ¹H NMR (400 MHz, CDCl₃) δ 1.27 (s, 3H), 1.37 (s, 3H), 1.67 (m, 2H), 1.83 (m, 3H), 2.15 (m, 3H), 2.37 (m, 1H), 2.53 (m, 1H), 2.70 (m, 2H), 5.11 (m, 1H), 5.41 (m, 1H), 5.65 (s, 1H), 5.79 (s, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.65 (dd, J = 8.3, 2.2 Hz, 1H), 8.06 (d, J = 2.2 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 16.9, 18.4, 21.8, 23.8, 37.1, 37.1, 37.5, 43.8, 46.5, 113.1, 123.5, 124.4, 130.8, 131.2, 139.4, 142.2, 154.5, 179.9, 198.4. IR (ATR) 3354, 3206, 2932, 1680, 1605, 1246, 901, 841 cm⁻¹. HRMS m/z: calcd. for C₂₀H₂₆NO₂ 312.1964 [M+H]⁺, found 312.1961.

**15-Hydroxy-7-oxoabieta-8,11,13-trien-18-oic acid (7).** A mixture of compound 1 (303 mg, 0.879 mmol) and KOH in ethylene glycol/water 10:1 (3.3 mL) was heated to 120 °C. After stirring the solution at 120 °C for 3.5 hours a 1 M aqueous solution of HCl (20 mL) Sawadjoon and ethyl acetate (25 mL) were added. The aqueous phase was extracted with ethyl acetate (2 × 25 mL), and the combined organic phases were washed with a 1 M aqueous solution of HCl (15 mL), water (15 mL), brine (15 mL) and dried over anhydrous Na₂SO₄. After removal of
the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel using dichloromethane in methanol (0→10%) as the eluent giving compound 11 (187 mg, 64%) as a yellowish solid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.27 (s, 3H), 1.36 (s, 3H), 1.57 (s, 3H), 1.58 (s, 3H), 1.66 (m, 1H), 1.83 (m, 4H), 2.38 (d, $J = 12.8$ Hz, 1H), 2.50 (d, $J = 15.1$ Hz, 1H), 2.72 (m, 2H), 7.36 (d, $J = 8.3$ Hz, 1H), 7.73 (dd, $J = 8.3$, 2.2 Hz, 1H), 8.06 (d, $J = 2.2$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 16.3, 18.2, 23.8, 31.7, 31.8, 36.6, 37.2, 37.4, 37.9, 43.7, 46.5, 72.5, 123.4, 123.8, 130.6, 130.8, 147.5, 153.9, 182.8, 198.8. IR (ATR) 3416, 2939, 2608, 1670, 1236, 1126, 752 cm$^{-1}$. HRMS m/z: calcd. for C$_{20}$H$_{27}$O$_3$ 331.1909 [M+H]$^+$, found 331.1909.

Cedrene (15): clear colorless liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1 0.84 (d, $J = 7.1$ Hz, 3H), 0.95 (s, 3H), 1.02 (s, 3H), 1.38 (m, 3H), 1.70 (m, 1H), 2.17 (m, 1H), 5.22 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 15.6, 24.9, 25.0, 25.8, 27.8, 36.2, 39.0, 40.8, 41.6, 48.3, 54.0, 55.0, 59.1, 119.3, 140.7. All analytical data are in agreement with literature values.24

4-Methyl-2,4-diphenyl-2-pentene (18): yellowish liquid. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.22 (s, 6H), 2.83 (s, 2H), 4.78 (m, 1H), 5.14 (m, 1H), 7.11 (m, 1H), 7.24 (m, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 28.9, 38.8, 49.7, 117.0, 125.6, 126.1, 126.6, 126.9, 127.9, 128.1, 143.6, 146.8, 149.5.

13-Propenyl-7-hydroxyabieta-8,11,13-trien-18-oic acid (27). A mixture of compound 2 (0.200 g, 0.613 mmol) and KOH in ethylene glycol/water 10:1 (2.1 mL) was heated to 120°C. After stirring the solution at 120°C for 3 hours a 1 M aqueous solution of HCl (7 mL) and ethyl acetate (20 mL) were added. The aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic phases were washed with a 1 M aqueous solution of HCl (10 mL), water (10 mL), brine (10 mL) and dried over anhydrous Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on
silica gel using ethyl acetate/ethanol (3:1) in hexane (0→100%) as the eluent giving compound 11 (156 mg, 80%) as a yellowish solid.

Compound 11 (0.110 g, 0.352 mmol) was dissolved in anhydrous methanol (2 mL) under argon followed by the addition of sodium borohydride (107 mg, 2.82 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1.5 hours. The solvent was carefully evaporated under reduced pressure, and the residue was diluted with ethyl acetate (10 mL) and a 1 M aqueous solution of HCl (5 mL) was added. The aqueous phase was extracted with ethyl acetate (2 × 10 mL), and the combined organic phases were washed with a 1 M aqueous solution of HCl (10 mL), water (10 mL), brine (10 mL) and dried over anhydrous Na₂SO₄. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel using ethyl acetate/ethanol (3:1) in n-heptane (0→100%) as the eluent giving compound 27 (42 mg, 37%) as a white solid. ¹H NMR (400 MHz, MeOD) δ 1.29 (m, 6H), 1.40 (m, 1H), 1.77 (m, 6H), 2.12 (m, 3H), 2.22 (m, 1H), 2.34 (m, 1H), 4.75 (t, J = 8.8 Hz, 1H), 5.02 (m, 1H), 5.34 (m, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.33 (ddd, J = 8.3, 2.1, 0.7 Hz, 1H), 7.62 (dd, J = 2.2, 0.9 Hz, 1H). ¹³C NMR (101 MHz, MeOD) δ 17.0, 19.5, 22.0, 25.7, 33.3, 37.8, 38.9, 39.3, 44.9, 48.2, 71.2, 111.9, 125.1, 125.6, 125.7, 139.1, 139.9, 144.6, 149.8, 182.1. IR (ATR) 3296, 2930, 2619, 1691, 1246, 999, 885, 825 cm⁻¹. HRMS m/z: calcd. for C₂₀H₂₅O₃ 313.1804 [M-H]⁺, found 313.1805.
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:……..

NMR spectra for compounds 2-4, 7, 10-13, 15, 18, 23, 24 and 27.

AUTHOR INFORMATION

Corresponding Author

*E-mail: vania.moreira@strath.ac.uk (V. M. M.)

ORCID

Vânia M. Moreira 0000-0001-6169-5035

Jari Yli-Kauhaluoma 0000-0003-0370-7653

Laura E. Kolsi 0000-0002-9975-9329

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

A L.K., V.M.M and J.Y.-K. acknowledge the University of Helsinki Research Foundation and the Academy of Finland (Projects 264020 and 265481) for financial support.
REFERENCES


(22) Fehn, S., Schwarz, S., Kempe, R. Regioselective heterodimerization of styrenes with diarylethene and vinylnaphthalene by a catalyst system consisting of simple acid and a ketone. *ChemistrySelect*, **2017**, *2*, 3289-3292.


Table of Contents Graphic (TOC)