

## Terpenoids as Renewable Nano-Sized Building Blocks

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## Abstract

Terpenoids are a large and structurally group of natural products containing multiple five carbon containing isoprene units. Previously we have reported that irrespective of their acyclic or alicyclic nature, all the triterpenoids containing 30C's have nano-metric lengths. In the current studies, detailed computations have been carried out with 120 naturally occurring mono- (C10), sesqui- (C15), di- (C20), sester- (C25), sesqua- (C35) and tetra- (C40) terpenoids

using Gaussian 09 software with Gauss view 07 and molecular mechanics calculation using Serena software. The heat of formation and the calculated molecular lengths obtained by the two methods were compared. Interestingly, monoterpene to tetraterpene all the terpenoids (except three monoterpene and one sesqui-terpene) have molecular lengths above one nanometer making them useful as nano-sized building blocks.

**Keywords:** terpenoid, renewable, nano, DFT, force field calculation, plant secondary metabolite

## 1. Introduction

Atomic theory was pioneered in 600 BCE by an ancient scientist, sage and philosopher Maharsi Kanada according to which every matter consists of an indestructible particle called atom.<sup>1</sup> Until 2016, the Periodic Table has 118 confirmed elements.<sup>2</sup> The covalent atomic diameters range from 1.06 Å for the smallest atom H to 4.50 Å for the largest atom Cs. For organic compounds which contain a C atom covalently linked to either another C or H or other elements such as N or O have covalent bond diameters of 1.54 Å, 1.50 Å, 1.46 Å for C, N and O respectively. Since the famous lecture by the Nobel Laureate physicist Richard Feynman in 1959 on the topic "*There's Plenty of Room at the Bottom*", scientists paid more attention to controlling individual atoms and molecules. Later, the term 'nanotechnology' was coined by Professor Norio Taniguchi in 1974 in his explorations of ultraprecision machining.<sup>3</sup> With the advent of scanning tunnelling microscope in 1981 and the invention of atomic force microscopy in 1983, manipulation of single molecule became possible. Although modern nanotechnology is believed to have started since the lecture by Professor Feynman and the term 'nanotechnology' used by Professor Norio Taniguchi, nanoscale materials were in use for centuries e.g., in the stained window glasses of Medieval churches. The colour of small gold particles appeared ruby red once the metal particle is smaller than around 30 nm in size. These Roman glassblowers found that glasses impregnated with gold chloride turned red during annealing probably due to reduction of the gold salt by carbon monoxide.

Nanoscience and nanotechnology are studies and application of small entities consisting of atoms and molecules having at least one of their dimensions within 1-100 nm. Whereas

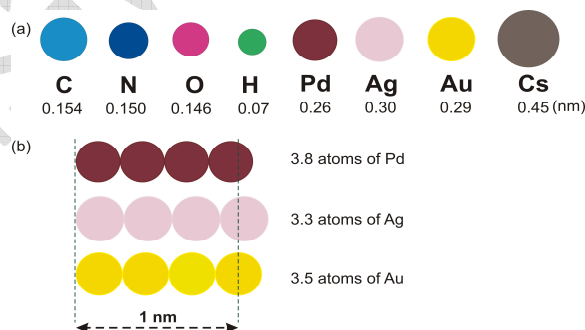


Figure 1: (a) covalent diameters of representative atoms in nm, (b) schematic representation of Pd, Ag and Au atoms needed for 1 nm length.

individual atoms can never fall within this range, when several atoms are kept side-by-side or for multiatomic molecules, the dimensions are likely to fall within this range. For example, with the covalent radii of 0.26, 0.30 and 0.29 nm for Pd, Ag and Au respectively, 3.8 atoms of Pd, 3.3 atoms of Ag and 3.5 atoms of Au should be placed side by side in a row for a 1 nm length (Figure 1b). For small hydrocarbons such as methane, ethane, propane, n-butane and the C5 isoprene, the molecular lengths obtained by DFT calculations are 0.42, 0.55, 0.67, 0.80 and 0.79 nm respectively (Figure 2). All these compounds remain in the gaseous state at room temperature.

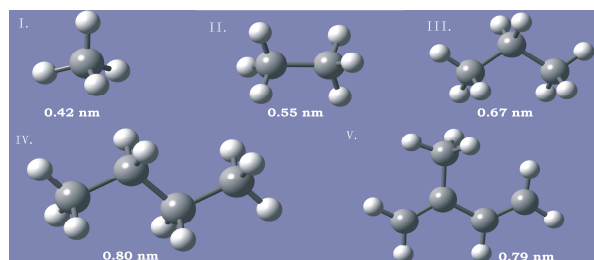
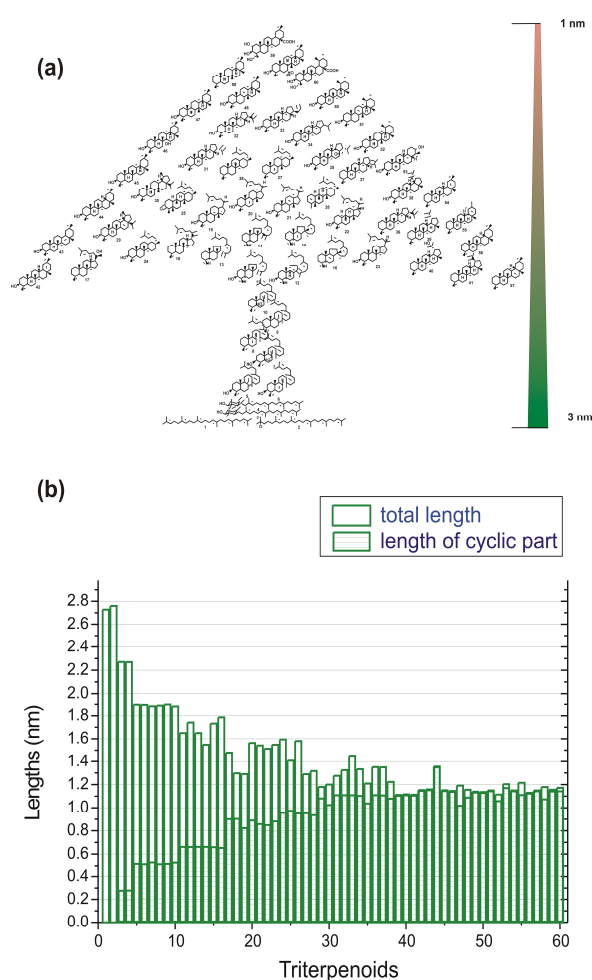


Figure 2: Energy minimized structures of methane, ethane, propane, n-butane and isoprene obtained by DFT calculation using Gaussian 09 software.

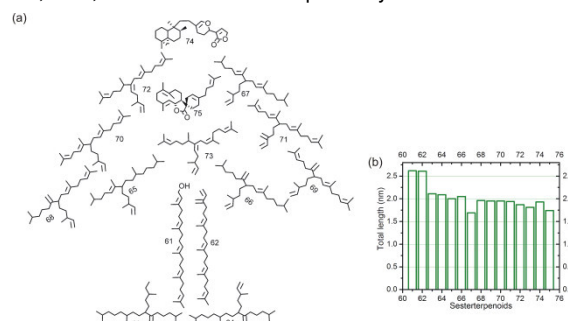


**Figure 3.** (a) Structures of the 60 naturally occurring triterpenoids used in force field calculations. Schematic representation of the variation of the lengths of the triterpenoids (right); (b) Calculated backbone lengths (nm) of sixty naturally occurring triterpenoids. The backbones of all the triterpenoids are 1.09 - 2.67 nm long. Squalene is 2.67 nm long and flexible. With increase in the number of the fused rings, the backbone lengths of the rigid part (shown by shading) increase with concomitant decrease in the flexible part. Adapted from ref.5 with permission of Springer.

Triterpenoids, the C<sub>30</sub> subset of the major plant secondary metabolite terpenoids, are a unique class of compounds

because of their highly diverse structures with different skeletons having varied rigid and flexible lengths. The inherently renewable nature of the compounds having one or more hydroxyl or carboxyl groups, very often with several centres of chirality have made this class of compounds a unique choice for their self-assembly studies in different liquids.<sup>4</sup> Detailed computations carried out with 60 representative triterpenoids have shown that all the triterpenoids have nanometric lengths (Figure 3).<sup>5</sup> The nanometric lengths are maintained even after folding. As the triterpenoids are extractable from plants, and triterpenoids with one or more hydroxyl and/or carboxyl groups are in common, the triterpenoids opened up a new era for the study of their self-assembly properties in different liquids. Seven triterpenoids namely arjunolic acid,<sup>6</sup> betulinic acid,<sup>7</sup> betulin,<sup>8</sup> oleanolic acid,<sup>9</sup> glycyrrhetic acid,<sup>10</sup> ursolic acid<sup>11</sup> and  $\alpha$ -onocerin<sup>12</sup> have been isolated from different plants and their self-assembly properties have been studied in different organic and aqueous binary solvent mixtures. Interestingly all the triterpenoids spontaneously self-assembled in the liquids yielding supramolecular structures of nano to micrometer dimensions such as vesicles, fibers, flowers, tubules, etc. The self-assemblies have utilized for the entrapment and of fluorophores, pollutant capture, generation of hybrid materials, etc. Inspired by these results, we became interested in studying the dimensions of the remaining terpenoids. Herein, we report the computational results with additional 120 representative of the other subset of terpenoids namely mono- (C<sub>10</sub>), sesqui- (C<sub>15</sub>), di- (C<sub>20</sub>), sester- (C<sub>25</sub>), sesqua- (C<sub>35</sub>) and tetra- (C<sub>40</sub>) terpenoids. Energy minimizations of all the 120 molecules were carried out using Gaussian 09 software with Gauss view 07 and molecular mechanics calculation using Serena software. The calculated heat of formation and the molecular lengths obtained by the two computational methods used were compared. Interestingly, with the exception of one sesquiterpene and three monoterpenoids, all the remaining 116 terpenoids were having lengths exceeding 1 nm. Thus terpenoids are nature's renewable nano gift.

isoprenoid alkenes 63 – 73<sup>13,14</sup> (Haslenes) have been isolated from *Haslea crucigera*, *Haslea pseudostrearia*, *Haslea saltstonica* and *Haslea ostrearia*. The lengths of these sesterterpenoids are 2.11, 2.09, 2.00, 2.05, 1.69, 1.96, 1.95, 1.95, 1.94, 1.87 and 1.87 nm respectively.



**Figure 4:** (a) Structures of naturally occurring sesterterpenoids used in DFT and force field calculations, (b) bar diagram of the lengths of the sesterterpenoids obtained by force field calculation.

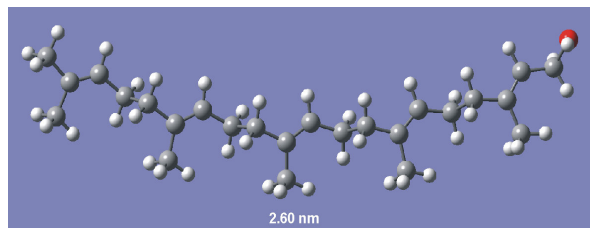


Figure 5. Energy minimized structure of a sesterterpenoid geranylfernesol **61** obtained by DFT calculation using the Gaussian 09 software.

## 2. Results and Discussions

### 2.1 Sesterterpenoids

Sesterterpenoids are a rear group of terpenoids having C<sub>25</sub> carbon skeleton, obtained from the widespread source of plants, marine sponge, insects and higher organism.

#### 2.1.1 Acyclic sesterterpenoids

Geranyl farnesol **61**<sup>15</sup>, the precursor of naturally occurring sesquiterpenoids is the major component of *Triticum aestivum* (wheat germ). The dehydrated molecules β Geranylarnesene **62**<sup>16</sup>, coming from **61** is the major compounds of *Nicotiana benthamiana*. These flexible sesterterpenoids are in 2.62 and 2.61 nm lengths respectively calculated by using force field model. The structures and distributions of branched isoprenoid alkenes 63 – 73<sup>17,18</sup> (Haslenes) have been isolated from *Haslea crucigera*, *Haslea pseudostrearia*, *Haslea saltstonica* and *Haslea ostrearia*. The lengths of these sesterterpenoids are 2.11, 2.09, 2.00, 2.05, 1.69, 1.96, 1.95, 1.95, 1.94, 1.87 and 1.87 nm respectively.

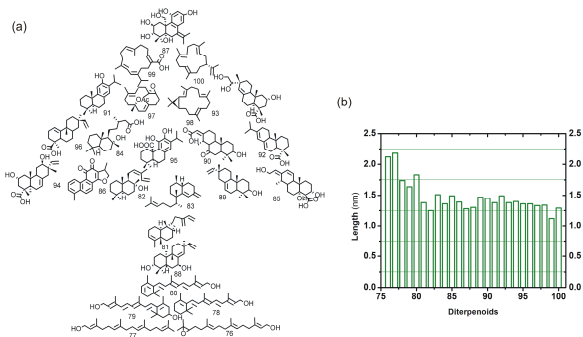


Figure 6: (a) Structures of naturally occurring diterpenoids used in DFT and force field calculations, (b) bar diagram of the lengths of the diterpenoids obtained by force field calculation

#### 2.1.2 Bicarboyclic sesterterpenoids

Bicarboyclic sesterterpenoids 25-deoxycacospongionolide **74** and Genopolide **75** were isolated from *Fasciospongia cavernosa*<sup>19</sup> and mountain wormwood

*Artemisia umbelliformis*<sup>20</sup> respectively. Lengths of these two sesterterpenoids are 1.93 and 1.74 nm respectively.

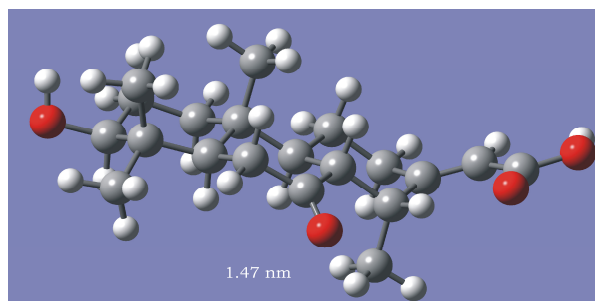


Figure 7. Energy minimized structure of a diterpene cassic acid **90** obtained by DFT calculation using the Gaussian 09 software

### 2.2 Diterpenoids

#### 2.2.1 Acyclic diterpenoid

Geranylgeraniol **76** and 14, 15-epoxygeranylgeraniol **77** the naturally occurring diterpenes are the major component of two different plants. Geranylgeraniol **76** was isolated from the seeds of *Bixa orellana*<sup>21</sup>. **76** was isolated from the *Pterodon emarginatus* Vog. Fruits<sup>22</sup>. These molecules are flexible and the lengths of these three diterpenoids have been calculated to be 2.12, 2.18 nm respectively.

#### 2.2.2 Monocyclic diterpenoid

Monocyclic diterpenoids retinol **78**, 3,4-dihydro retinol **79** and 3- hydroxy retinol **80** are commonly known as Vitamin A1, Vitamin A2 and Vitamin A3, isolated from different type of plants like Pink grapefruit, Apricots, Carrots, Pumpkin, Sweet potatoes, Winter squash, Dark green, leafy vegetables, Broccoli etc.<sup>23,24</sup> The molecules are flexible and 1.64-1.83 nm long.

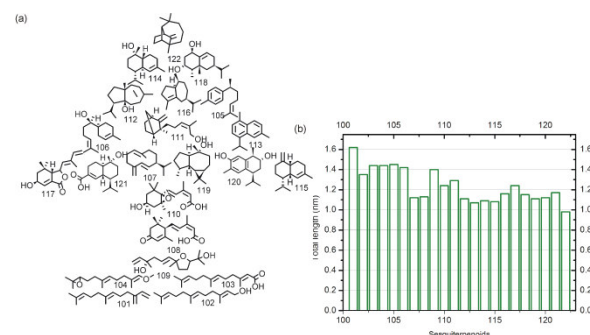


Figure 8: (a) Structures of naturally occurring sesquiterpenoids used in DFT and force field calculations, (b) bar diagram of the lengths of the sesquiterpenoids obtained by force field calculation

#### 2.2.3 (6-6) Bicyclic diterpenoid

Bicyclic diterpenoid Terpentetriene **81** and cis-Abienol **82** were isolated from *Boswellia carterii*<sup>25</sup> and *Abies*

*balsamea*.<sup>26</sup> Elisabethatriene **83** and Labdanolic acid **84** were isolated from the *Pseudopterogorgia elisabethae*<sup>27</sup> and Resins from *Copaifera species* respectively.<sup>28</sup> Because of the trans fusion at the ring junction, the bicyclic naturally occurring diterpenes are rigid. The lengths of the bicyclic diterpenoids are 1.25 – 1.38 nm including the Van der Waal radius.

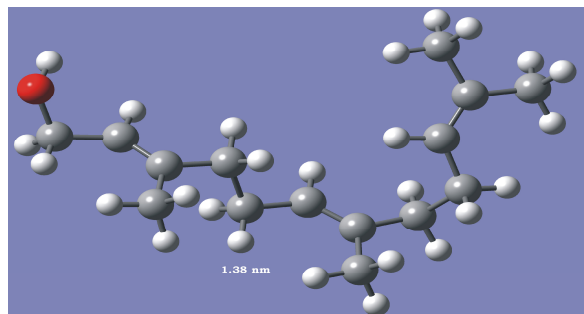


Figure 9. Energy minimized structure of sesquiterpenoid Farnesol **102** obtained by DFT calculation using the Gaussian 09 software.

## 2.2.4 (6-6-6) Tricyclic diterpenoid

Arbusculic acid **85** was isolated from *Calcarisporium arbuscula*<sup>29</sup>. The tricyclic diterpene **86** was isolated from *Salvia miltiorrhiza*<sup>30</sup>. Plebeianiol A **87** was isolated from *Salvia plebeian*<sup>31,32</sup>. Rice (*Oryza sativa*) produces a variety of labdane type diterpenoids, Oryzalexin A **88** was isolated from the *Oryza sativa*<sup>33</sup>. Akhdarenol **89** and Cassic acid **90** were isolated from Aerial parts of *Aeollanthus rydingianus*<sup>34</sup> and *Erythrophleum* alkaloid<sup>35</sup> respectively. Ferruginol **91** and Abietic acid **92** were extracted from *Chamaecyparis pisifera*<sup>36</sup> and Pine wood smoke<sup>37,38</sup> respectively. Wulingzhic acid A **93** and Wulingzhic acid B **94** both were isolated from *Trogopteris Feces*<sup>39</sup>. Carnosic acid **95** was extracted from *Rosmarinus* and *Salvia* plant<sup>40</sup> extracts. Stachyrosane **96** was extracted from *Stachysparviflora*<sup>41,42,43</sup>. These twelve tricyclic diterpenes are 1.25 – 1.51 nm long with a rigid cyclic part and the flexible side chain.

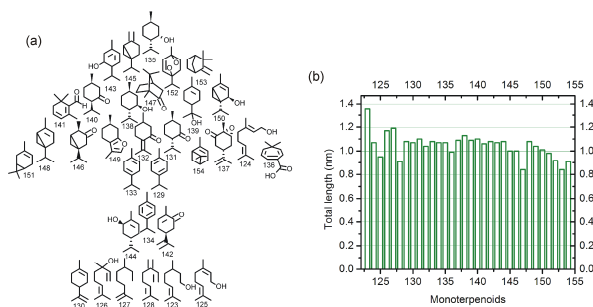


Figure 10: Figure 6: (a) Structures of 32 naturally occurring monoterpenoids used in DFT and force field calculations, (b) bar diagram of the lengths of the monoterpenoids obtained by force field calculation.

## 2.2.5 Macrocyclic diterpenoid

Cembrane typediterpenoids have been found in various resins. Thus microphyllanin **97** was found from the resin of the North American *Bursera microphylla* (Burseraceae)<sup>44</sup>. Casbene **98** was found from the *Ricinus communis*<sup>45</sup>. Another naturally occurring two Cembrene type diterpenoid crotocebraneic acid **99** and neo cembrene **100** are a natural macrocyclic diterpenoid isolated from *Croton oblongifolius* roxb<sup>46</sup> and corals of the genus *Nephthea*<sup>47</sup> respectively. These four cembrene type macrocyclic diterpenoid are 1.12 – 1.34 nm long with a flexible cyclic part.

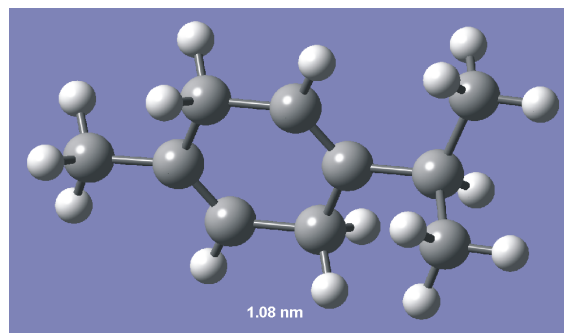


Figure 11. Energy minimized structure of monoterpene  $\alpha$ -phellandrene **129** obtained by DFT calculation using the Gaussian 09 software

## 2.3 Sesquiterpenoids

### 2.3.1 Acyclic sesquiterpenes

According to the biogenetic isoprene rule, all the sesquiterpenoids are synthesized from farnesol<sup>56</sup>. Acyclic sesquiterpenoids farnesene **101**<sup>48</sup>, farnesol **102**<sup>49</sup>, farnesoic acid **103**<sup>49</sup>, juvenyl hormone **104**<sup>50</sup> are isolated from plants like *Cotton plants*, *Peaches*, *tomatos*, *Corpus Allatum* respectively each of having lengths 1.62 nm, 1.35 nm, 1.44 nm, 1.44 nm respectively.

### 2.3.2 Monocyclic sesquiterpenoids

Monocyclic sesquiterpenes (+) curcumene **105**<sup>51</sup>,  $\square$ -bisabolol **106**<sup>52</sup>, germacrene **107**<sup>53</sup>, abscisic acid **108**<sup>54</sup>, neginufural **109**<sup>55</sup>, cis-xanthoxin **110**<sup>56</sup>,  $\square\square$ santalol **111**<sup>57</sup> were isolated from plants named *Lantana camara* leaves, *Salviasosifolia*, *Cichoriumintybus*, Peaplants, *Vitex negundo*, Tomato shoots, *Santalum genus* each of having length 1.45 nm, 1.42 nm, 1.12 nm, 1.13 nm, 1.40 nm, 1.24 nm, 1.29 nm respectively.

### 2.3.3 Bicyclic sesquiterpenoids:

Bicyclic sesquiterpenes carotol**112**<sup>Error! Bookmark not defined.</sup>, cadalene **113**<sup>58</sup>,  $\square\square$ cardinol **114**<sup>59</sup>,  $\square$ -muurolene **115**<sup>Error! Bookmark not defined.</sup>, acyphyllene **116**<sup>60</sup>, hostanolide **117**<sup>61</sup>, capsidol **118**<sup>Error! Bookmark not defined.</sup>, globulol **119**<sup>62</sup>, calamenane **120**<sup>63</sup>, dysodensiol D **121**<sup>63</sup> were isolated from plants Carrot, Grapes, *Aframomummo legueta*, *Mentha piperita*, *Hosta ensata*, *Capsicum frutescens*, *Eucalyptus globulus* Labill,

*Kadsura longipedunculata* and *Oxylum densiflorum* each of having lengths 1.11 nm, 1.07 nm, 1.09 nm, 1.08 nm, 1.16 nm, 1.24 nm, 1.15 nm, 1.11 nm, 1.12 nm and 1.17 nm respectively.

### 2.3.4 Tricyclic sesquiterpenoids :

Tricyclic sesquiterpene longifolene **122**<sup>64</sup> is isolated from Red clover leaves having length 0.98 nm.

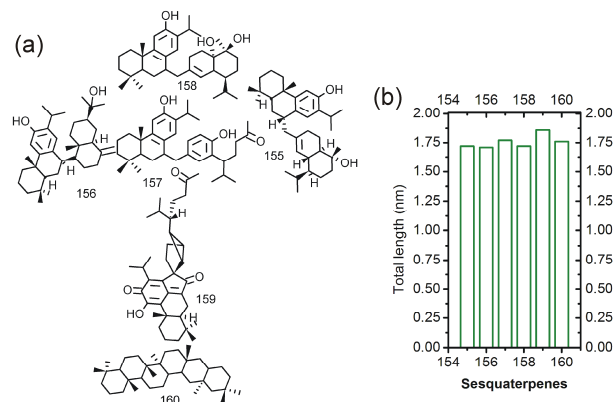


Figure 12: (a) Structures of sesquiterpenoids used in force field calculation, (b) bar diagram of the lengths of the sesquiterpenoids obtained by force field calculation

## 2.4 Monoterpenoids

### 2.4.1 Acyclic monoterpenoids

According to the biogenetic isoprene rule, all the terpenes are being biosynthesized from isopentenyl diphosphate (IPP) or its epimer dimethylallyl diphosphate (DMPP). Monoterpenoids named citronellol **123**, geraniol **124**, nerol **125**, linalool **126**, 2,6-dimethyloctane **127**, myrcene **128** are isolated from different plants such as *Rosa hybrid*<sup>65</sup>, *Pelarginium graveolens*<sup>66, 65</sup>, *Rosa dilecta*<sup>65</sup>, *Muscata Grapes*<sup>67</sup>, *Salvia officinalis*<sup>68, 69</sup>. All the acyclic monoterpenoids are flexible and the lengths have been calculated to be 1.36, 1.07, 0.95, 1.17, 1.19, 0.91 nm respectively.

### 2.4.2 Monocyclic monoterpenoids

Monocyclic monoterpenes □-phellandrene **129**, limonene **130**, (-)-menthone **131**, pulegone **132**, □-terpinene **133**, p-cymene **134**, (+)-neomenthol **135**, thujic acid **136**, □□□-epoxycarvone **137** were isolated from plants such as *Curcuma longa* L.<sup>70</sup>, *Pippermint*<sup>76</sup>, *mangifera indica*<sup>71</sup>, *Mentha piperita*<sup>76</sup>, *Mentha spicata* Linn<sup>72</sup>, *Salvia officinalis*<sup>69</sup>, *Organum vulgare*<sup>73, 74</sup>, *Mentha piperita* Leaves<sup>76</sup>, essential oils of *Carum carvi*<sup>75</sup> respectively. The other monocyclic monoterpenoids like (-)-menthol **138**, (+)-isomenthone **140**, S (+)-carvone **142**, carveol **144** are present in *Mentha piperita*<sup>76, 77</sup>, □□-terpinol **139** is present in *genus chinopodium*<sup>78</sup> and safranal **141** were isolated from *crocus sativus* L.<sup>79</sup> The molecules are having length 1.08, 1.07, 1.1,

1.04, 1.08, 1.07, 1.07, 0.99, 1.09, 1.13, 1.09, 1.10, 1.06 nm respectively.

### 2.4.3 Bicyclic monoterpenoids

Bicyclic monoterpenoids □-Thujone **146**, camphore **147**, □-thujene **148**, camphene **153**, □-pinene **154** is isolated from *Salvia officinalis*. (+)-menthofuran **149**, umbellouol **150**, car-3-ene **151**, ascaridole **152** was isolated from *Croton regelianus*<sup>80</sup>. *Mentha piperita*<sup>76</sup>, *Thymus capitatu* respectively. The lengths of the bicyclic monoterpenoids are 1.00, 1.00, 0.84, 1.08, 1.04, 1.01, 0.98, 1.06, 0.84, 0.91 nm respectively.

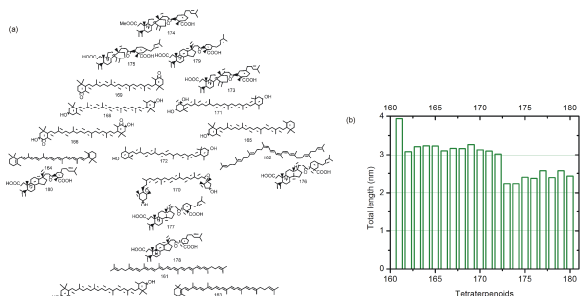


Figure 14: (a) Structures of tetraterpenoids used in force field calculation, (b) bar diagram of the lengths of the tetraterpenoids obtained by force field calculation

## 2.5 Sesquiterpenoids

### 2.5.1 Tricyclic sesquiterpene

Tricyclic sesquiterpene Ferrugicadinol **155** and Ferrugieudesmol **156** where isolated from the bark of *Calocedrus macrolepis var formosana*<sup>81</sup> and Sugikurojins I **157** and Sugikurojins G **158** where isolated from the bark of *Cryptomeria japonica*.<sup>82, 83</sup> The lengths of these sesquiterpens have been calculated to be 1.72, 1.71, 1.77, 1.72 nm respectively.

### 2.5.2 Hexacyclic sesquiterpene

Hexacyclic sesquiterpene Cryptotrione **159** were isolated from the bark of *Cryptomeria japonica*<sup>84</sup> and Ficusquaterpene **160** were isolated from the leaves of *Ficus nitida* Thunb.<sup>85</sup> The length of the sesquiterpene have been calculated to be 1.86 and 1.76 nm respectively.

## 2.6 Tetraterpenoids

### 2.6.1 Acyclic tetraterpenes

Lycopene **161** and Hexahydrolycopene **162** are naturally occurring tetraterpenes isolated from plants *Solanum lycopersium*<sup>86</sup> and *Carica papaya*<sup>87</sup> respectively. Both the molecules are flexible and length of these two molecules have been calculated to be 3.9 and 3.1 nm respectively.

### 2.6.2 Monocyclic tetraterpenes:

Gama carotene **163** extracted from *Blakeslea trispora*<sup>88</sup> is mostly flexible and lengths is 3.21 nm.

### 2.6.3 Bicyclic tetraterpenes

Bicyclic tetraterpenes Beta carotene **164** is obtained from *Solanum lycopersium*<sup>86</sup>, Beta cryptoxanthin **165** extracted from *Persimmons*<sup>89</sup>. Astaxanthin **166** and Lutein **167** are isolated from *Spinacia cleracea*<sup>90</sup> and *Haematococcus pluvialis*<sup>91</sup> respectively. Zeaxanthin **168** is obtained from *Citrus simensis*.<sup>90</sup> Canthaxanthin **169** isolated from *Chlorella zofingiensis*<sup>92</sup>. Capsanthin 5,6 epoxide **170** is obtained from *Asparagus falcatus*.<sup>93</sup> Retrocarotenoid **171** and Eschscholtzathin **172** are extracted from *Eschscholtzia californica*.<sup>94</sup> Their lengths are varied from 3.26 nm to 3.02 nm.

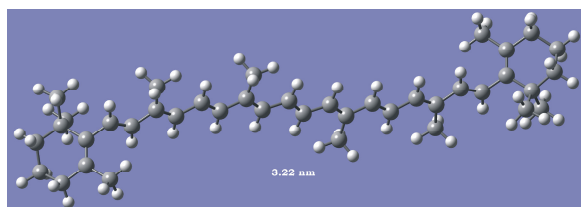


Figure 15. Energy minimized structure of a tetraterpenes  $\beta$ -carotene obtained by DFT calculation using the Gaussian 09 software

### 2.6.4 Tetracyclic tetraterpene:

Tetracyclic tetraterpene Abibalsamin A to H **173 - 180** are extracted from *Abies balsamea*.<sup>95</sup> Their lengths are 2.234 nm to 2.57 nm.

## 3. Conclusions

DFT and force field calculations carried out with 120 naturally occurring terpenoids have shown that except one diterpenoid and three monoterpene, all the remaining terpenoids have molecular lengths exceeding 1 nm. Plant metabolites being inherently renewable in nature, and thousands of terpenoids being isolable from plants, the terpenoids offer tremendous opportunities for their use as renewable nano-sized building blocks in diversified areas of science and technology for the development of a sustainable society.

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