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UNUSUALLY PENDANT-PRENYLATED CYCLIC TERPENOIDS – AN EMERGING CLASS OF NATURAL PRODUCTS WITH A BROAD SPECTRUM OF BIOLOGICAL ACTIVITY

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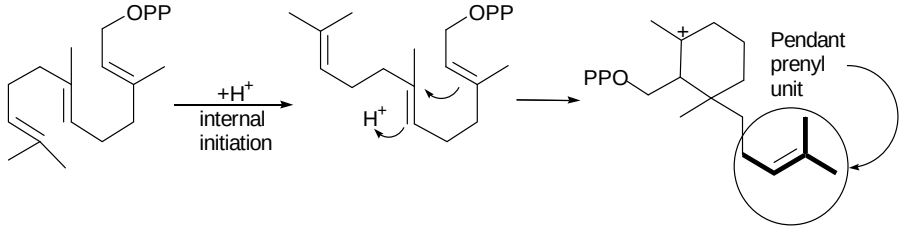
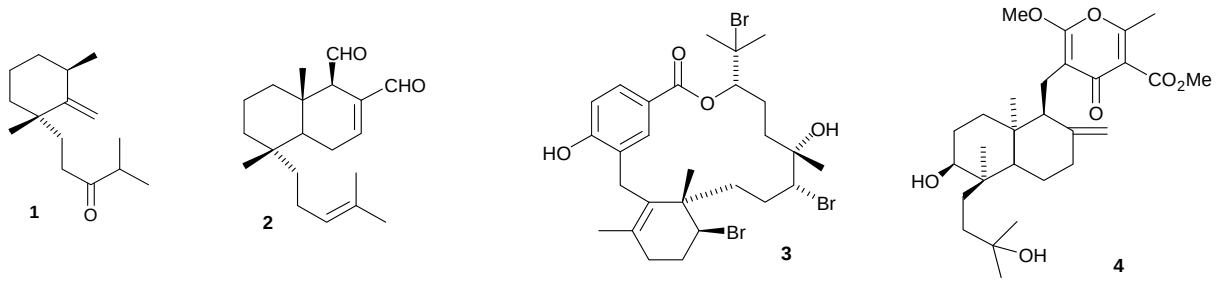
Terpenoids represent a large family of natural products with an impressive diversity of carbon skeletons and functionalisation pattern. The cyclization-isomerization processes play a crucial role in this diversity spanning.

To date, there are two basic biogenetical mechanisms of terpene cyclization. The first one includes nucleophilic attack of a double bond belonging to the open chain precursor to the C1 carbon, elimination of the pyrophosphate anion and following transformation of the formed carbonium ion either by successive cyclisations/rearrangements or proton elimination. The second cyclization mechanism includes interaction of an external electrophile, usually with a terminal double bond in the chain, followed by the electrophilic attack of the formed carbonium ion to the following double bonds and leading to monocyclic or polycyclic compounds.

But a separate group of terpenes derive from the interaction of the electrophile (a proton or equivalent onium- ions) with internal double bonds of the open terpenic chain. This cyclization mechanism leads to partially cyclised products with the terminal prenyl chain attached pendant to the cyclic backbone.



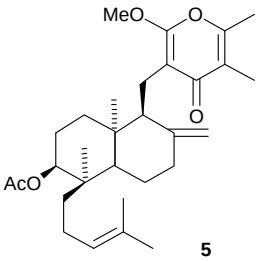
Such "unusually" cyclized terpenoids have been sporadically reported from different natural sources, starting basically from the mid 70-th of the last century. Initially, there were compounds of sacculatane family, isolated from liverworths of different origin. But the last 10 years witnessed an increasing number of such examples and more cyclic terpenes with the pendant □-terminus are isolated from both terrestrial and marine sources.



The first example of a natural sesquiterpenoid with pendant prenylation was tridensone **1**, isolated in 1992 from the liverwort Bazzania tridens [1]. Other sesquiterpenic pendant prenylated compounds include axinyssane family, riccardiphenols, chenopodenes, meta- and hypochromins.

The largest group of terpenes possessing a specific pendant prenylation are represented by diterpenoids. The first representative named sacculatal **2** has been reported in 1977 as a secondary metabolite of the liverworth *Tricholeopsis sacculata* [2]. The systematic investigation of briophites led to the discovery of numerous sacculatanes with different functionalization

pattern. On the other hand, marine organisms have also delivered a whole plethora of saculatanic compounds, including chlorinated, methylated and rearranged compounds. Other pendant prenylated diterpenes include dactylomelane family, punctatene and its acetate, infuscatrienol and magydardiendiol related compounds. A very interesting family of terpenes similar to bromophycolide A **3** was reported from the red alga *Callophycus serratus* [3].



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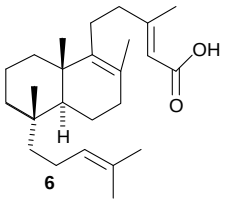

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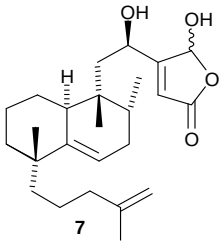

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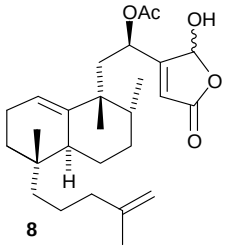

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The presence of a heterocyclic fragment is biogenetically connected to other relevant groups of bicyclic diterpenes with pendant prenylation, containing also an additional pyrone ring. The representative examples include colletotrichin A **4** and nalanthalide **5**.

The first representative of sesterterpenoids posessing a pendant prenylation was disideapalaunic acid **6** [4]. Relevant sesterterpenoids with pendant prenylation are dysidiolide **7** and related cladocorane **8**. The biological activity profile of these compounds has stimulated numerous synthetic and SAR studies.

One of the families related to triterpenes of mixed biogenetical origin are adociasulfates, isolated for the first time from the sponge *Haliclona* (*aka Adocia*) sp [5]. The biological activity of adociasulfates is related to their ability to disrupt the transport of stabilized microtubules by kinesin motor proteins.

The current report attempts to summarise the known-to-date representatives of terpenoids with such an unusual prenylation pattern and own contribution to the biomimetic chemical synthesis of compounds with pendant isoprene units attached to cyclic frameworks.

References:

1. C. Wu, C. Chen, *Phytochemistry*, **1992**, 31, 4213-4217.
2. Y. Asakawa, T. Takemoto, M. Toyota, T. Aratani, *Tetrahedron Lett*., **1977**, 18, 1407-1410.
3. J. Kubanek, A. C. Prusak, T. W. Snell, R. A. Giese, K. I. Hardcastle, C. R. Fairchild, W. Aalbersberg, C. Raventos-Suarez, M. E. Hay, *Org. Lett*., **2005**, 7, 5261–5264.
4. H. Hagiwara, H. Uda, J. Chem. Soc., *Chem. Commun*., **1988**, 815-817.
5. C. L. Blackburn, C. Hopmann, R. Sakowicz, M. S. Berdelis, L. S. B. Goldstein, D. J. Faulkner, *J. Org. Chem*., **1999**, 64, 5565-5570.