Hedycaryol – Central Intermediates in Sesquiterpene Biosynthesis, Part II

Houchao Xu\textsuperscript{[a]} and Jeroen S. Dickschat\textsuperscript{*}[a]
Abstract: The known sesquiterpenes that arise biosynthetically from hedycaryol are summarised. Reasonings for the assignments of their absolute configurations are discussed. The analysis provided here suggests that reprotonations at the C1=C10 double bond of hedycaryol are directed toward C1 and generally lead to 6–6 bicyclic compounds, while reprotonations at the C4=C5 double bond occur at C4 and result in 5–7 bicyclic compounds. Read more in the Review by H. Xu and J. S. Dickschat (DOI: 10.1002/chem.202200405).

1. Introduction

Terpenoids represent the largest class of natural products, exhibit an extraordinary structural diversity and complexity, and are often associated with remarkable biological and pharmaceutical activities.[1] Their carbon skeletons are assembled through the action of terpene synthases from only a few acyclic precursors, oligoprenyl diphosphates, that contain multiples of five carbon units with an alkene function and a methyl branch and follow the general formula H-(C5H8)n-OPP (Scheme 1A). During the past decades, many type I terpene synthases have been characterised from plants,[2–4] bacteria,[4,5] fungi,[4,6] and protists[7] that act on their substrates through diphosphate abstraction, followed by a cationic cascade reaction to yield usually (poly)cyclic terpene hydrocarbons or alcohols. Subclasses of these enzymes include monoterpene synthases for the conversion of geranyl diphosphate (GPP, C10, n=2) and sesquiterpene synthases that act on farnesyl diphosphate (FPP, C15, n=3). For diterpene and sesterterpene synthases[4,8] the substrates geranylgeranyl diphosphate (GGPP, C20, n=4) and geranyl farnesyl diphosphate (GFPP, C25, n=5) with their multiple reactive double bonds allow for highly complex cyclisation cascades, leading to a fascinating structural complexity from a simple acyclic molecule in just one enzymatic step. Site-directed mutagenesis experiments gave detailed insights into terpene synthase catalysis and made enzymes with new functions available,[9] and also the conversion of non-natural substrate analogues is possible,[10] making terpene synthases particularly interesting for the enzymatic synthesis of molecules with highly complex architectures. Finally, heterologous expression approaches in engineered yeast[11] or Escherichia coli[12] strains add to the successful methodical repertoire of modern terpene synthase applications.

Type I terpene synthases ionise oligoprenyl diphosphates through the abstraction of diphosphate to yield a highly reactive allyl cation that can subsequently undergo a cascade reaction composed of several elementary steps including cyclisation reactions by intramolecular attack of an alkene function to a cationic centre, Wagner-Meerwein rearrangements, hydride or proton shifts, and a final deprotonation or capture with water. In some cases the deprotonation to an electrically neutral compound is followed by a reprotonation event to initiate a second cyclisation cascade. Herein, for the deprotonation-reprotonation sequence combined experimental and theoretical studies have revealed the importance of main chain carbonyl oxygens and an active site water for the bacterial selinadiene synthase.[13,14]

For the conversion of FPP by sesquiterpene synthases different initial cyclisation events are possible (Scheme 1B).[15,16] After ionisation of FPP to the farnesyl cation (A), a 1,10-cyclisation can lead to the (E,E)-germacradienyl cation (B) or a 1,11-cyclisation may result in the (E,E)-humulyl cation (C).

Scheme 1. Terpene biosynthesis. A) Structures of oligoprenyl diphosphates. B) Cyclisation modes of FPP towards sesquiterpenes.
Alternatively, the abstracted diphosphate can re-attack at C3 to give nerolidyl diphosphate (NPP) that can undergo a conformational change through rotation around its C2-C3 single bond. Its reionisation to D opens four more cyclisation options through 1,10-cyclisation to the (Z,E)-germacradienyl cation (E), 1,11-cyclisation to the (Z,E)-humulyl cation (F), 1,6-cyclisation to the bisabolyl cation (G) and 1,7-cyclisation to H. For all chiral intermediates both enantiomers can be reached through these processes.

Intermediate B can be deprotonated to yield germacrene A that is a widespread intermediate towards many eudesmane and guaiane sesquiterpene hydrocarbons that can be formed through its reprotonation-induced transannular reactions. The accumulated knowledge about this class of sesquiterpenes was recently summarised by us in a review article in this journal.[17] We have also performed a computational study to explore the chemical space through downstream hydride shifts for the different stereoisomers of the guaianes, showing that (suprafacial) 1,2-hydride shifts are always possible, while 1,3-hydride migrations can only be realised for certain geometries of the guaiane skeletons.[18] As an alternative to the deprotonation to germacrene A, cation B can also be captured by water to yield the sesquiterpene alcohol hedycaryol, which is a likewise important intermediate toward many sesquiterpene alcohols. Here we provide a comprehensive overview of the chemistry of hedycaryol and the compounds derived from it through terpene cyclase mediated downstream cyclisations.

2. Hedycaryol

2.1. Structure elucidation and occurrence in Nature

Without detailed knowledge about its structure, in 1916 Semmler and Liao discovered the first monocyclic sesquiterpene alcohol elemol (2, Scheme 2A) that was isolated from a fraction of the essential oil of the Philippine tree *Canarium luzonicum* (elemi) obtained by fractional distillation.[19] After establishment of its constitution by Sorm and coworkers,[20] the compound was also found to be the main constituent (60%) of the essential oil from *Hedycarya angustifolia*, a small tree native to Australia.[21] The missing optical activity of the chiral compound geijerene (4), the main constituent in the steam distillates from *Geijera parviflora*, was explained by Jones and Sutherland through their discovery that pregeijerene (3) is the true plant natural product that undergoes a Cope rearrangement during compound isolation.[22] Subsequently, the same workers also described 2 as the product of a thermal Cope

![Scheme 2.](image-url)
rearrangement of hedycaryol (1). The absolute configuration of 2 has been established independently by chemical correlations to tetrahydroaussurea lactone and (+)-10-epi-α-cyperone (5) in a procedure involving epimerisation of the side chain attached to C7 (Scheme 2B). Reduction of 5 with Li in ammonia gave trans-fused 6 that was converted with isopropanol acetate and p-TsOH into enol ester 7, followed by ozonolysis and esterification to 8. Reduction with LiAlH4 via ketalisation with ethylene glycol gave 9 that was easily epimerised under acidic conditions to 10. Its reaction with MeMgl via protection of the alcohol functions as tetrahydropyran-3-yl (THP) ethers yielded 11, which was subjected to both Me groups attached to 10-membered ring up, D and 25 were obtained through hydroboration and oxidation of 2.

Elemol (2) was later reisolated from various plants including Juniperus sabina and J. scopulorum. Chamaecyparis obtusa, Citrus sinensis and C. nobilis, Saussurea lappo, Cinnamomum camphora, Fokienia hodginsii, Calycanthus floridus, Bunium circulare, Gingko biloba, Amryis baissamifera, Canarium zeylanicum, Bothriocloa intermedia, Comimphora abyssiicatica, Santolina oblongifolia, Cymbopogon proximus, Eremophila flaccida, Piper ribesoides, Monocyclusanthus vignei, Neocallitropsis pancheri, Cryptomeria japonica, and Eucalyptus maculata, which demonstrates the widespread occurrence of 1 in nature. After its first report from H. angustifolia, 1 compound was subsequently also isolated from the undistilled oils of the plants Phelodium ozoanthamnoides, Rubus rosifolius, Thujaopsis dolabrata, Thymus praecox, Cryptomeria japonica and C. fortunei, and Chamaecyparis obtusa. For the optical rotation of 2 low negative values between [α]D = −2 and −9.7 are given in the literature, while for 1 positive values between [α]D = +24.5 and +32.7 were reported. The enantiomer (−)-1 is only known from the bacterial hedycaryol synthase (HCS) from Kitasatospora setae (αS) whose Cope rearrangement gives (−)-2 (αS) whose Cope rearrangement gives (−)-2 (αS). This finding reflects the observation that also in other cases bacteria and fungi produce the enantiomers of plant terpenes.

Because of its strained 10-membered ring 1 exists as a mixture of three conformers 1a with both Me groups attached to the ring up (UU) and crossed double bonds, and 1b and 1c with parallel double bonds and each one Me group up and one down (DU, UD) (Scheme 3). Their fairly slow interconversion causes line broadening in the NMR spectra, and therefore the NMR data assignment was a long standing problem that was only recently solved through a 13C- and stereoselective 2H-labelling approach. Complete NMR data for 2 have also been published. The structure and absolute configuration of (−)-1 have been further secured by an enantiomeric synthesis from (−)-guaiol.

2.2. Biosynthesis, enzymatic and non-enzymatic cyclisation

The biosynthesis of 1 by type I terpene synthases proceeds through the abstraction of diphosphate from FPP to initiate a 1,10-cyclisation and attack of water to C11 (Scheme 4A). Selective hedycaryol synthases for 1 are known from the plants Populus trichocarpa (PTPS7), Camellia brevistyla (CbTPS1), and Liquidambar formosana (LFTPS01), in all cases with undetermined absolute configuration, and for (−)-1 from Kitasatospora setae whose product was initially erroneously assigned as (2Z,6E)-hedycaryol; for this bacterial enzyme also a crystal structure is available. In addition, the diterpene synthase VenA from Streptomyces venezuelae that converts GGPP into venezuelene A has a reported side activity with FPP as hedycaryol synthase. For the diterpene synthase spiroviolene synthase from Streptomyces violens ancestral sequence reconstruction resulted in a functional switch to a hedycaryol synthase. As will be discussed in detail in this review article, 1 is an important biosynthetic intermediate, as exemplified by its reported biotransformation into cryptomeridol (12) by a mortared root suspension of chicory (Cichorium intybus). Hedycaryol (1) is also a proposed intermediate in the biosynthesis of eudesmane-2x,11-diol (13), the product of the sesquiterpene synthase ZmEDS from Zea mays. Herein, the downstream enzymatic cyclisations of 1 are initiated by reprotonation, however, care has to be taken to distinguish enzymatic from non-enzymatic transformations, as it is well known that 1 can also undergo an efficient non-enzymatic acid

![Scheme 3](image_url)

**Scheme 3.** Conformers of 1. U = Me group at 10-membered ring up, D = Me group down. „Crossed” and „parallel” refers to relative orientations of double bonds.

![Scheme 4](image_url)

**Scheme 4.** A) Biosynthesis of 1 from FPP and its conversion into 12 and 13. B) Acid-catalysed reaction to eudesmols 14–16.
catalysed transannular reaction to yield a mixture mainly composed of α-, β- and γ-eudesmol (14 - 16, Scheme 4B).\textsuperscript{23,72,73} Terpene synthases can further convert 1 into eudesmols or guaiols through the protonation induced reactions shown in Scheme 5. Reprotonation of 1 at C1 can lead to I, the precursor to eudesmols, while the alternative reprotonation at C4 results in the secondary cation J that is disfavoured. For guaiols either a protonation at C4 to K or at C10 to L are possible. The subsequent sections will give a detailed discussion of known compounds arising from 1 via these reactions.

Scheme 5. Possible terpene cyclisation modes for 1.

Scheme 6. Cyclisation reactions of 1 induced by reprotonation at C1 towards intermediates I1-I8.

3. Eudesmols

3.1. Cyclisation modes from hedycaryl to eudesmols

Eudesmols can arise from (\(+\))-1 through protonation at C1 that can induce the cyclisation to the four stereochemically distinct intermediates I1-I4 (Scheme 6). The corresponding protonation induced cyclisations from (\(-\))-1 gives rise to their enantiomers I5-I8. All these intermediates can potentially react by three alternative deprotonations, addition of water or intramolecular attack of the hydroxy function at the cation. Further compounds can be formed, if first a 1,2-hydride shifts occurs that may be followed by skeletal rearrangements.

3.2. Eudesmols from cation I1

Cation I1 can undergo deprotonations to yield α-eudesmol (14), β-eudesmol (15) or γ-eudesmol (16, Scheme 7A). Ruzicka and coworkers demonstrated that the initially obtained “eudesmol” was a mixture of 14 and 15 of varying composition, which explained the observed variations in melting points and optical rotations.\textsuperscript{74} Their separation from Eucalyptus macarthurii was first reported by McQuillan and Parrack in 1956. While the separation of 14 and 15 through chromatography on alumina or repeated recrystallisation could not fully be achieved, crystallisation of the 3,5-dinitrobenzoate esters and their saponification gave access to the pure compounds, establishing positive optical rotations for 14 (\([\alpha]_D^0 = +28.6\)) and 15 (\([\alpha]_D^0 = +63.8\)).\textsuperscript{75} The same study also reported on the γ-isomer 16 (\([\alpha]_D^0 = +62.5\)) that was obtained from (\(-\))-selinene dihydrochloride (17) by elimination and hydrolysis.\textsuperscript{76} The absolute configuration of 15 was established by Woodward and coworkers through correlation with the steroids.\textsuperscript{76} All three eudesmols 14–16 yield the same hydrogenation product (\(-\))-18, confirming their consistent absolute configurations.\textsuperscript{75} Further proof for this assignment was obtained by synthesis of eudesmols 14–16 from (\(-\))-dihydrocarvone (19).\textsuperscript{25,78}

The alcohols 14–16 were frequently obtained as a mixture from various plants including different Eucalyptus species,\textsuperscript{29,80} Thuja occidentalis\textsuperscript{81,82} and Phebalium ozothamnoides,\textsuperscript{81} while the pure compounds were isolated from Callitropsis araucarioides,\textsuperscript{82} Cordia trichotoma,\textsuperscript{83} and Cryptomeria japonica.\textsuperscript{48} Finally, 14 was also isolated from the lichens Porella perrottetiana, but in this case the material showed a negative optical rotation (\([\alpha]_D^0 = -6.9\)).\textsuperscript{84} The suggested revision of the optical rotation of 14 with the structure as shown in Scheme 7A from a positive to a negative value, based on a synthetic transformation of (\(-\))-15 into (\(+\))-14\textsuperscript{85} conflicts all previous consistent chemical correlations. Also a later study reported a negative optical rotation for 14 obtained by total synthesis from (\(-\))-carvone (20).\textsuperscript{85} Despite the unclear situation, the structure of 14 is currently assigned with a negative optical rotation to CAS number 473–16-5. Final conclusions require further investigations (cf. also discussion in Section 3.6. about ent-14 derived from 15). Pterocarpus santalinus is a reported source of pure (\(+\))-15, but its comparably low optical rotation (\([\alpha]_D^0 = +36.0\)) may point to a contamination.
with (+)-14.[86] All three compounds 14–16 have been isolated from Neocallichitropsis pancheri with full assignment of ^1H and ^13C NMR data.[87]

Through the attack of water to the cationic centre in I1 two diastereoisomeric diols, cryptomeridiol (12) and 4-epi-cryptomeridiol (21), can be formed. Cryptomeridiol (12) was first isolated from Widdringtonia dracomontana, but first only reported as a “dior” of negative optical rotation ([α]D = −24).[87] It was subsequently reisolated from Fokienia hodginsii, shown to be identical to 12 from W. dracomontana by IR spectroscopy and an unchanged melting point upon admixture of an authentic sample, and its structure identified albeit with unspecified configuration at C4. The structural identification mainly relied on the conversion into (+)-17 with gaseous HCl and correlated the compound to the same enantiomeric series as the eudesmols.[88] After a third isolation from Cryptomeria japonica 12 was named cryptomeridiol and its structure fully assigned by correlation with β-eudesmol (15) that was converted into 12 by epoxidation with monoperphthalic acid and treatment with LiAlH4 (Scheme 7B).[89] A more modern version of this synthesis using mCPBA for the epoxidation step was published in 1994.[90] Its identity with 12 from W. dracomontana and from F. hodginsii was not immediately recognised, possibly because of a typographical error in the given name for 12 as “selina-4,7-diol”[90] that should read “selina-4,11-diol”, but subsequently shown by IR and mixed melting point.[91] Also proximadiol, the anti-spasmodic principle from Cymbopogon proximus,[92,93] was later shown to be identical to (−)-12.[94,95] Another interesting transformation that secures the absolute configuration of cryptomeridiol is the conversion of (−)-2 into (−)-12 by oxymercuration and reductive workup (Scheme 7C).[96]

The diol 12 is fairly widespread in the plant kingdom and has additionally been isolated from Artemisia pygmaea,[97] Magnolia obvata,[98] Drymis winteri,[99] Hedychium spicatum,[100] Thuja polaris,[101] Carissa edulis,[102] Chamaecyparis pisifera,[103] Juglans mandshurica[104] and Achillea clupeolata,[105] in all cases with a reported negative sign for the optical rotation. Compound (−)-12 was also obtained in a biotransformation of synthetic (+)-1 with a mortared root suspension of chicory.[76] A terpene synthase for 12 (of undetermined absolute configuration) is known from Tripterygium wilfordii (TwCS).[106] However, the surprisingly widespread occurrence of this compound in many plants may also point to a non-enzymatic formation from (−)-1 in an acid catalysed reaction e.g. during chromatographic purifications, especially if water is present.[76] or during steam distillation. This was impressively shown by steam distillation of plant leaves containing (−)-1 in the presence of H2O, leading to incorporation of the ^16O-label into 12 and its epimer 21.[107] Fully assigned ^1H- and ^13C NMR data were reported for 12 from the plant Blumea balsamifera. For unclear reasons this paper shows the enantiomer of (−)-12.[108]

The epimer 4-epi-cryptomeridiol (21) was first isolated from Amanoa oblongifolia ([α]D = +3.8)[110] in comparison to [α]D = +26.1 for the synthetic compound obtained from (+)-15.[96] The same enantiomer (−)-21 was later reisolated from Chamaecyparis pisifera[104] and Canarium ovatum.[111] Cryptomeria japonica[112] and Citrus hystrix.[113] Fully assigned ^13C NMR data have been reported for synthetic 21.[86]

Cation I1 can undergo a 1,2-hydride shift to M1 that can either react by deprotonation to eudesm-5-en-11-ol (23), by capture with water to (−)-eudesmane-5,11-diol (24), by intramolecular attack of the alcohol function to 4-epi-cis-dihydroagarofuran (25), by Wagner-Meerwein rearrangement (WMR) to N1 and deprotonation to (−)-ermoligenol (26) or its isomer 27, or by WMR to O1 and deprotonation to (−)-hinesol (28, Scheme 8). Only few reports are available for 23 that was first isolated from Helichrysum italicum[113] and later from Balnea sarmientoi.[114] Unfortunately, both studies did not report on the optical rotation of 23 and its absolute configuration has not formally been established, while fully assigned NMR data were given in both cases.[111,114] The diol 24 was first obtained synthetically from (−)-γ-eudesmol (16) by photochemical

Scheme 7. A) Eudesmols derived from I1 and related compounds. B) Chemical correlation of (±)-15 with (−)-12 and C) of (−)-2 with (−)-12.
Eudesmols derived from I1 and 1,2-hydride shift to M1.

The rearranged compound eremoligenol (26) was first isolated from Ligularia fischeri ([α]D = –93.5) and its absolute configuration was established by correlation to (+)-eremophilenol (31) through a sequence of hydroboration and oxidation to the ketone 30, followed by Huang-Minlon reduction, dehydration and catalytic hydrogenation (Scheme 9B). The compound was later reisolated from Europs sulcatus[119] and Oreodaphne porosa.[120] The isomer 27 was first obtained as a synthetic material[121] followed by its isolation from Alpinia japonica ([α]D = –14.9).[122] (−)-Hinesol (28) was first reported from Atractylodes lancea ([α]D = –40.2) and shown to be a constituent of “attractylol” that was initially believed to be a pure compound.[123] Its structure was initially wrongly assigned,[124] but later corrected with a suggested absolute configuration based on its co-occurrence with (−)-β-eudesmol (15).[125] This assignment was later confirmed by a correlation with (−)-δ-selinene (32) that was obtained from 28 by formic acid catalysed rearrangement and dehydration (Scheme 9C), albeit not in pure form,[126] and by an enantioselective synthesis of (−)-28.[127] Hinesol shows an antitrypanosomal activity against Trypanosoma brucei.[128]

3.3. Eudesmols from cation I2

Cation I2 could potentially lead to the alcohols 33–35 by deprotonation or to the diols 36 and 37 by addition of water (Scheme 10). For 33 only a synthesis of the racemate has been reported,[129] while 34 ([α]D = −17.5) has been synthetised enantioselectively from (+)-intermedeol[130] but both compounds are not known from natural sources. Also 10-epi-γ-eudesmol (35) was first obtained from synthesis of dihydrocarvone (+)-19, unfortunately without reporting the optical rotation of 35,[131] but the first isolation paper mentions the identity of (−)-35 from vetiver oil (Vetiveria zizanioides) and the synthetic material.[132] The compound was also isolated from Amyris balsamifera,[133] Aquilaria malaccensis ([α]D = −68.8),[133] Alpinia japonica,[132] Hedychium spicatum[134] and Bursera graveolens.[133]

Chem. Eur. J. 2022, 28, e202200405 (7 of 20) © 2022 The Authors. Chemistry - A European Journal published by Wiley-VCH GmbH
The diol 36 was also first synthesised,\textsuperscript{134} followed by an isolation from \textit{Ursinia trifida};\textsuperscript{137} in both cases without mentioning the optical rotation. At the same time the isolation of a compound from \textit{Plucheia arguta} with same \textsuperscript{13}C NMR data (apart from C4, this is likely a typographical error), but with a cis-decalin structure (10-epi-36) was reported ([\(\delta\)\textsubscript{C} \textsuperscript{13} = +66.66].\textsuperscript{138}

This erroneous structural assignment was later corrected based on a total synthesis of (\(+\)-36) ([\(\delta\)\textsubscript{C} \textsuperscript{13} = +73.3) from (\(+\)-dihydrocarveone (19)).\textsuperscript{139} Pterodondiol from \textit{Laggera pterodonta} for which initially a structure with 7S configuration were established by correlation with (\(+\)-rossifolius, but this time with a reported negative optical (Scheme 12A),\textsuperscript{140} was later demonstrated by X-ray crystallography.\textsuperscript{142} Compound 36 is additionally known from \textit{Goniolobalol tapisoides}.

\textsuperscript{13}C NMR data of 36 have been published in CDCl\textsubscript{3} and in C\textsubscript{6}D\textsubscript{6}.\textsuperscript{146} Compound 37 is unknown.

Rearranged compounds from I2 (Scheme 11) can be accessed by a 1,2-hydride shift to M2, from which a deprotonation leads to (\(+\)-rossifoliol (38), a capture with water to (\(-\)-39), and the intramolecular attack of the hydroxy function to (\(-\)-dihydro-\(\beta\)-agarofuran (40). A methyl migration to N2 and deprotonation can result in (\(+\)-valerianol (41) or (\(-\)-jinkohemerol (42), while ring contraction to O2 and deprotonation lead to (\(-\))-agarospirol (43). Most of these compounds are fairly widespread.

Rossifoliol (38), \([\delta\)\textsubscript{C} \textsuperscript{13} = +105, was first isolated from \textit{Rubus rosifolius},\textsuperscript{144} after its possible formation along the lines of Scheme 11 had been proposed.\textsuperscript{145} Its structure and absolute configuration were established by correlation with (\(-\)-40 (Scheme 12A),\textsuperscript{141} and also the X-ray crystal structure has been obtained.\textsuperscript{146} The alcohol 38 was also found in \textit{Phonus arborescens}, but this time with a reported negative optical rotation that was not commented on ([\(\delta\)\textsubscript{C} \textsuperscript{13} = -17.1].\textsuperscript{147} Also the \textsuperscript{13}C NMR data differ substantially,\textsuperscript{144,147} leaving doubt if the material from \textit{P. arborescens} is indeed identical to the originally isolated rosifoliol. The diol 39 was so far only isolated from \textit{Alpinia japonica} ([\(\delta\)\textsubscript{C} \textsuperscript{13} = -21.8],\textsuperscript{148} and its structure was secured by synthesis from (\(-\)-10-epi-\(\alpha\)-cyperone (ent-5) that proceeded by epoxidation with mCPBA and epoxide opening with ketone reduction using LiAlH\textsubscript{4} and AlCl\textsubscript{3} to yield 10-epi-\(\gamma\)-eudesmol (35, Scheme 12B). Selective \(\beta\)-epoxidation with VO(acac)\textsubscript{3} and tBuOOH followed by epoxide opening with LDA gave 44 that was catalytically hydrogenated with Wilkinson’s catalyst to obtain (\(-\)-39 (\([\delta\)\textsubscript{C} \textsuperscript{13} = -46.2].\textsuperscript{149}

Dihydro-\(\beta\)-agarofuran (40, \([\delta\)\textsubscript{C} \textsuperscript{13} = -77.0), was first isolated from fungus-infected agarwood (\textit{Aquillaria agallocha}) with unknown configuration at C4 and the configurations at C5 and C7 determined wrongly.\textsuperscript{150} The structure was later revised based on a synthesis from ent-5 that gave the diene 45 upon reduction with LiAlH\textsubscript{4} and pyrolysis in the presence of basic alumina (Scheme 12C). Photosensitised oxygation to peroxide 46 was followed by isomerisation to the hydroxy

\begin{align*}
\text{Scheme 11. Eudesmols derived from I2 and 1,2-hydride shift to M2.}
\end{align*}
ketone 47 under mildly basic conditions. Treatment with acid-washed Al₂O₃ resulted in ring closure to 48, that upon reduction to a stereoisomeric mixture of allyl alcohols with NaBH₄, conversion into the allyl chlorides with SOCl₂ and reduction with LiAlH₄ gave α-agarofuran (49).

At this stage the previous work had shown that 49 can be obtained from β-agarofuran (50) by ozonolysis and addition of MeLi to 51, followed by dehydration with SOCl₂ in pyridine (Scheme 13A). It was also known that the catalytic hydrogenation of 49 and 50 leads to materials with slightly different properties, with the compound obtained from 50 being identical to natural (−)-40. The two compounds 40a and 52a were suggested to be stereoisomers, but their configurations at C4 were unclear. A later erroneous correlation with valencene through biotransformation resulted in a confusion of these stereoisomers, but the situation was ultimately resolved by a synthesis of (−)-isodihydroagarofuran (52) from 53 (Scheme 13B). This route proceeded through oxymercuration to 54. Treatment with NaOMe in MeOH gave a mixture of mainly 55 and small amounts of 56, with 55 being convertible into 56 under acid catalysis with p-TsOH. Reduction with p-toluenesulfonyl hydrazine and NaBH₄ resulted in (−)-52 that was identical to the product obtained by catalytic hydrogenation of 49, and consequently also the structure of 40 (−)-epi-52 was secured. The absolute configuration of (−)-40 was evident from its correlation to (−)-δ-selinene formed upon treatment with BF₃ etherate (Scheme 13C). The ether (−)-40 was also isolated from Galbanum resin, Alpinia japonica, Lagerra alata and Vetiveria zizanioides.

(−)-Valeranol (41) was first isolated from Valeriana officinalis ([α]D = +134) and its absolute configuration was established by dehydration with SOCl₂ or POCl₃ yielding a hydrocarbon that was identical with (−)-valencene (57, Scheme 14A). It is also known from Amyris balsamifera and agarwood, and is the main product of the G411 A enzyme variant of ZEA møy s eudesmanediol synthase (ZmEDS). Kusunol that was reported from Cinnamomum camphora is identical to (−)-41 ([α]D = −76) to (−)-Jinkoheremol (42) was first isolated from agarwood and its structure was determined by NMR spectroscopy. Further proof for the assigned structure was given by catalytic hydrogenation that yielded a mixture of the same epimeric dihydro-compounds as obtained from 41. The absolute configuration was tentatively assigned by comparison of its optical rotation ([α]D = −66) to values for structurally similar compounds, but has not been formally established by chemical correlation. (−) Agarospirol (43) was first isolated from Aquilaria agollocha ([α]D = −5.7) with a suggested structure of ent-hinesol (ent-28), based on a biosynthetic relation to dihydro-β-agarofuran with the at that time assumed structure of 58 (Scheme 14B). The same paper suggested 43 as an alternative stereochemical representation. Notably, after the structural revision of dihydro-β-agarofuran to 40 (151,155) an analogous biosynthetic relation can indeed explain 43 (Scheme 14C). A synthesis of (rac)-28 also excluded this structure for agarospirol (163) while later syntheses of (rac)- and (−)-43 confirmed its structure and

Scheme 13. Chemical correlations. A) Conversion of 50 into 49 and catalytic hydrogenations. B) Synthesis of (−)-52 from 53. C) Absolute configuration of (−)-40 by correlation with (−)-β-selinene (32).

Scheme 14. Chemical correlations. A) Dehydration of (−)-41 to (−)-57. B) Hypothetical structure for agarospirol (ent-28) based on an assumed biosynthetic relation to dihydro-β-agarofuran with the initially reported structure of 58. C) Revised structure of 40 for dihydro-β-agarofuran and analogous biosynthetic relation to the correct structure 43 of agarospirol.
absolute configuration. A later report about agarwood constituents claims a reisolation of (−)-43, but shows the structure of ent-28. Neuroleptic properties have been described for 42 and 43 in mice which may be responsible for the sedative effects of agarwood.

3.4. Eudesmols from cation I3

The structures of the eudesmols that can directly be formed from I3 by deprotonation (59, 60, and 35), capture with water (61 and 62) or intramolecular attack of the alcohol to the cation (63) are shown in Scheme 15. Compound 35 has already been discussed above as a deprotonation product from I2 (Scheme 10).

(+)-Dihydrooccidentalal (59), [α]D20 = +59.2, is not known as a natural product, but was obtained by catalytic hydrogenation from (+)-occidentalal (64, Scheme 16A), a constituent of Thuja occidentalis for which the structure was assigned by detailed analysis of coupling constants in the 1H NMR spectrum. The compound is also formed from (+)-occidentalal (Scheme 16A), a constituent of Thuja occidentalis with fully established structure by 2-dimensional NMR techniques, but neither the optical rotation has been reported nor the absolute configuration has been assigned. The diols 61 and 62 are unknown from natural sources and have only been obtained by synthesis of their racemates. The ether (−)-4,11-epoxy-cis-eudesmane (63, [α]D20 = −22) is a major constituent of the frontal gland secretions of the termite Amitermes evunci fer. Its structure was first correctly assigned based on a series of microreactions and later confirmed by an enantioselective synthesis from (−)-carvone. Compound 63 was later also isolated from Amitermes excellens and from A. minimus, in which case the paper erroneously shows the opposite absolute configuration, but still reports a negative optical rotation ([α]D20 = −34). Interestingly, (−)-63 has a repellent activity against the ant Crematogaster californica. The same ether 63 is also known from the plant Phorus arborescens.

Further compounds from I3 (Scheme 17A) can be reached by a 1,2-hydride shift to M3 and capture with water to 13 or intramolecular attack of the alcohol to (−)-52 for which structure elucidation has already been discussed above. The diol 13 ([α]D20 = −9.0) was so far only isolated from Cymobopogon distans with structure elucidation based on NMR spectroscopy and X-ray crystallography, and is the main product of Zea mays eudesmanediol synthase (ZmEDS). The absolute configuration was evident through a synthesis from 35 (prepared as shown in Scheme 12) by epoxidation and reductive epoxide opening (Scheme 17B). Isodihydroagarofuran (52), also named δ-dihydroagarofuran, was isolated from Phorus arborescens, Bursera graveolens, and identified in the cyanobacterium Calothrix by GC/MS in comparison to standards of 52 and its stereoisomer 40, albeit without determination of absolute configuration.

3.5. Eudesmols from cation I4

Little is known about eudesmols from cation I4 (Scheme 18). The alcohols 66 ([(α)]D20 = −41.1) and 67 ([(α)]D20 = +21.16) were only obtained by synthesis. The erroneous assignment of structure 66 to a sesquiterpene diol from Pluchea arguta and its structural revision to 36 have been discussed above. Compounds that are accessible after 1,2-hydride shift to M4

A)

B)

Chem. Eur. J. 2022, 28, e202200405 (10 of 20)
include the diol 68 that is unknown from natural sources, but has been obtained by synthesis together with its C4 epimer without further structural assignment regarding the stereochemistry at C4.[115] Intramolecular attack of the alcohol function to the cation in M4 gives access to (−)-cis-dihydroagarofuran (69) that was so far only isolated from Prostanthera ovalifolia ([α]D25 = 87.6). Its relative configuration was determined by 2-dimensional NMR techniques and direct comparison to its stereoisomers 40 and 52, while the absolute configuration was evident from its dehydration to (+)-δ-selinene (32, boxed in Scheme 18).[179]

Methyl group migration from M4 to N4 and deprotonation gives access to (−)-5-epi-jinkoheremol (71) for which recently a terpene synthase from Catharanthus roseus (CrTPS18) was discovered.[180] The absolute configuration of 71 was determined by a comparison of measured to calculated ECD curves. Notably, 71 was shown to be the biosynthetic precursor of debneyol (72) by a genetically clustered cytochrome P450 monooxygenase (CYP71D349),[180] which is in contrast to the earlier findings for the biosynthesis of 72 that showed incorporation of radioactivity from the sesquiterpene hydrocarbon 5-epi-aristolochene (73).[181] Alternatively, N4 can be deprotonated to 70, which is unknown as a natural product, but the racemic compound has been synthesised.[182]

3.6. Eudesmols from cation I5

Generally, the number of reports on compounds from the enantiomeric series derived from (−)-hedycaryol through cations I5 - I8 is much lower than those discussed above for (−)-hedycaryol derivatives. Compounds that could biosynthetically directly arise from I5 (Scheme 19) include (−)-α-eudesmol (ent-14) for which only one synthetic report is available. Herein, the absolute configuration was secured by MoKα X-ray crystallography of the p-bromobenzoate-epoxide of ent-14 (Flack parameter: 0.030(3)) and the optical rotation of ent-14 was found to be positive (([α]D25 = +6.4)[183]) which supports the suggested revision of the signs of optical rotation for the enantiomers of 14.[84] The freshwater fungus Beltriana rhombica is a source of ent-15 (([α]D29 = −37.9)[184]) and (+)-cryptomeridiol (ent-21) has been reported from the cypress Chamaecyparis obtusa,[180] while ent-16 and ent-22 are unknown. No natural products obtained from I5 through 1,2-hydride shift and eventually skeletal rearrangement are known.

3.7. Eudesmols from cation I6

Compounds that can directly arise from I6 are summarised on Scheme 20. The sesquiterpene alcohol 7-epi-α-eudesmol (ent-33) was first claimed from Amyris balsamifera. The absolute configuration was concluded from the positive optical rotation (([α]D = +10)[186]) but since at that time no reference data of...
either enantiomer had been reported, the reason for this assignment is unclear. Notably, all other related compounds from this plant have the usual 7R configuration.\textsuperscript{[40]} \textit{7-epi-\textgamma-}
Eudesmol (ent-35) was first reported with a negative optical rotation ($[\alpha]_{D}^{25} = -15$) from Cryptomeria japonica.\textsuperscript{[48]} This work describes structure elucidation by NMR, but does also not explain the reasoning for the assignment of absolute configuration. Subsequently, ent-33 was also reported from Laggera alata without stating the optical rotation, together with ent-34 and ent-35 for which again negative optical rotations were given.\textsuperscript{[59]} However, this conflicts previous assignments based on enantioselective syntheses of (−)-34 and, from (+)-dihydrocarvone, of (−)-35 (cf. Section 3.3).\textsuperscript{[130-132]} The situation becomes even more confusing, because a later synthesis study reported the transformation of (−)-dihydrocarvone into (−)-ent-35 ($[\alpha]_{D}^{10} = -30.1$).\textsuperscript{[187]} Taken together, the assignments of optical rotations especially to the enantiomers of 35 are doubtful and await future clarification. \textit{7-epi-\textalpha-Eudesmol} (33) has also been observed as the product of a bacterial sesquiterpene synthase from \textit{Streptomyces viridochromogenes}.\textsuperscript{[43,48]} Homologs of this enzyme can be found in many streptomycetes.\textsuperscript{[189]} The absolute configuration of 33 from \textit{7-epi-\textalpha-eudesmol} synthase is undetermined, but the enantiomer ent-33 would possibly fit best for a bacterial compound as bacteria often produce the opposite enantiomer as observed in plants.

For isodonesquitin A from \textit{Isodon grandifolia} the structure of ent-36 was assigned, but the positive optical rotation ($[\alpha]_{D}^{28} = +24.6$) is in conflict with this assignment,\textsuperscript{[190]} because a total synthesis of both enantiomers gave $[\alpha]_{D}^{19} = -66.7$ for ent-36 and $[\alpha]_{D}^{29} = +73.3$ for 36. The measurements also revealed a strong concentration dependency of these data, but always gave the same sign of optical rotation for the same enantiomer.\textsuperscript{[199]} Unfortunately, the isolation paper from \textit{I. grandifolia} did not further discuss the problem of absolute configuration assignment,\textsuperscript{[190]} and thus the assignment may likely be in error in this study. After a first assignment of the structure of 67 to a diol from \textit{Pluchea arguta}\textsuperscript{[188]} a revision based on synthetic work suggested the compound to be ent-36,\textsuperscript{[90]} but after synthesis of both enantiomers it was ultimately demonstrated that 36 is the correct structure.\textsuperscript{[199]} \textit{Pluchea quitoc} is also a reported source of ent-36,\textsuperscript{[191]} giving a reference to its isolation and first structural revision.\textsuperscript{[90,138]} With the correction of the absolute configuration for the compound from \textit{P. arguta}\textsuperscript{[190]} it must be concluded that also \textit{P. quitoc} is a producer of 36. Taken together, despite some discussions about ent-36 from natural sources in the literature, it seems that this compound is not known as a natural product. Also no reports are available for its C4 epimer ent-37. (−)-ent-Rosifoliol (ent-38) can arise from 16 by 1,2-hydride shift and deprotonation and has been described from the liverwort \textit{Calypogeia muelleriana}.\textsuperscript{[192]}

### 3.8. Eudesmols from cation 17

Eudesmols potentially arising from cation 17 are shown in Scheme 21. Starting with a report about the composition of the essential oil from \textit{Elionurus elegans}\textsuperscript{[195]} compound ent-59 ("S-

\textit{epi-7-epi-\textalpha-eudesmol") is mentioned in several GC/MS based studies, but has never been isolated, which leaves doubt about the absolute configuration assignment and most if not all these studies may indeed have detected 59 instead. This view is in line with the fact that also neither ent-60, ent-61 and ent-62 nor any compounds arising from 17 by 1,2-hydride shift and eventually skeletal rearrangement have ever been reported. In summary, no secure reports about natural products from 17 are available.

### 3.9. Eudesmols from cation 18

Only very little is known about eudesmol derivatives arising through cation 18 (Scheme 22). The knowledge is basically limited to the fungal phytotoxin hypodoratoxide. After the initially assigned structure of 74\textsuperscript{[194]} was corrected to that of 75,\textsuperscript{[195]} the biosynthesis was investigated through feeding experiments with isotopically labelled precursors. Starting from 18, a 1,2-hydride shift leads to M8 that can be deprotonated to ent-69, a cometabolite of 75 in \textit{Hypomyces odoratus}. A methyl migration to N8, skeletal rearrangement to P8 and intra-
molecular attack of the alcohol function to the cation result in 75.\[195\] The absolute configurations of 69 and 75 in *H. odoratus* have not firmly been established.

4. Guaiols

4.1. Cyclisation of hedycaryol by protonation at C4

Hedycaryol (\(+\)-1) can undergo cyclisations through protonation at C4 towards four stereoisomeric intermediates K1–K4 (Scheme 23). The series of opposite enantiomers K5–K8 is analogously accessible through protonation induced cyclisations from (\(-\)-1), but no natural products with unequivocally established absolute configurations from these intermediates with 75 configuration appear in the literature. In all cases H5 and Me15 are trans to each other because the addition to the E configured C4=C5 double bond of hedycaryol is necessarily anti. The following sections discuss all known natural products that can be formed from the K stereoisomers either directly by deprotonation, capture with water or intramolecular attack of the alcohol function, or after hydride shifts.

4.2. Guaiols from cation K1

Guaiols that can be formed directly from K1 are shown in Scheme 24A. (\(+\)-)Bulnesol (76) from guaiacwood oil (\([\alpha]D_20^\circ = +3.8\)]\[196\]) is one of the most important representatives of the class of guaiols. Its structure was elucidated by Sorm in a correlation to guaiol (89, Scheme 25A) that yielded the same hydrogenation product as 76.\[196–198\] It was later also isolated from *Galbanum* resin\[196\] and *Neocalitropsis pancheri*,\[47\] and a sesquiterpene synthase from *Thapsia lacinia* for the production of 76 and 89 as main products (TlTPS509) with compound isolation by preparative GC and NMR based structure elucidation was described.\[200\] The alcohol 5αH-guai-9-en-11-ol (77) was recently reported from guaiacwood oil,\[114\] while the diol (\(-\)-)78 (\([\alpha]D_{25}^\circ = -25.0\)) is known from the extremophilic fungus *Pithomyces* isolated from a mine waste pit.\[201\] The absolute configuration of 78 has not formally been established yet. Starting from K1 a 1,2-hydride shift to Q1 and deprotonation explain 79 that has also recently been found in guaiacwood oil.\[114\] The ether 80 can arise from Q1 by a second 1,2-hydride shift to R1 and intramolecular attack of the alcohol function, but is only known as a synthetic compound that was obtained from its 4-epimer (\(-\)-)83, a known natural product from *Ligularia* (\([\alpha]D_{25}^\circ = -45\), Scheme 24B).\[202\] Bromination at C4 with NBS and elimination gave 84 that upon catalytic hydrogenation yielded 80,\[203\] thereby completing the set of all eight stereoisomers with 7R configuration (for discussion of other stereo-
isomers see below). A 1,3-hydride shift from K1 to R2 and deprotonation yield the alcohol 82 from guaiacwood oil,[114] while ring closure gives guaioxide (81) that will be discussed in detail in the next section.

### 4.3. Guaiols from cation K2

Compounds from K2 are summarised in Scheme 25A. As an alternative to its formation from K1, bulnesol (76) could also be formed from K2 by deprotonation, which may better explain its co-occurrence with guaiol (89), the lead compound from the class of hedycaryol derived 5–7 membered bicyclic sesquiterpene alcohols, that can also be formed from K2 by 1,2-hydride shift to Q2 and deprotonation. Guaiol was first described from guaiacwood by Gandurin ([α]D20 = -26.64) as a bicyclic tertiary alcohol with one double bond.[200] The compound is widespread and has also been isolated from Callitris intratropica,[204] Eucalyptus maculata,[205] Drimys lanceolata,[206] Cinnamomum camphora,[207] Callitris columellaris,[208] Guillonea scabra,[209] Thapsia villosa,[210] Canarium luzonicum (Manila elemi),[211] Murraya gleinei,[212] Neocallitropsis pantheri,[213] Eriostemon fitzgeraldii,[214] Ferula fuleroides[215] and Uvaria puguenensis,[216] and is a product of the above-mentioned terpene synthase TTPS509 from Thapsia laciniata.[206] After establishment of its constitution,[217] the absolute configuration was clarified by chemical correlation.[196,198,218,219]

Other known compounds that can directly arise from K2 include cis-guai-9-en-11-ol (85) from Galbanum resin ([α]D20 = +4.9) [214] and from guaiacwood oil that is also a source of 10,11-epoxyguaiane (88),[114,177] The diol 87 was first isolated from Leuceria floribunda with the relative configuration secured by NOE experiments,[220] and later reported again from Jatropha curcas.[221] Starting from Q2, a second 1,2-hydride shift to R3 and deprotonation leads to 90. This compound is known from guaiacwood oil[114] and has been synthesised from guaiol (89),[222] (-)-Guaioxide (81, [α]D9 = -38.2) easily formed by acid treatment of 89 (Scheme 25B).[222,223] It has also been isolated from guaiacwood oil, but may have been formed during the isolation process.[177] Its hypothetical biosynthesis requires a 1,3-hydride shift from K1 to R2 and intramolecular attack of the alcohol function (Scheme 24A). The stereoisomer 1-epi-guaioxide (91) can arise analogously from R3, but is not known as a natural product (Scheme 25A). Both compounds have been synthesised from 89 by oxidation with Pb(OAc)4, to yield 92, followed by catalytic hydrogenation to 91 and (-)-81 (Scheme 25B).[225] Guaioxide (81) has also been correlated to dihydroguaio, the hydrogenation product of 89, by a combination of microbial and chemical transformations.[226]

### 4.4. Guaiols from cation K3

Guaiols from K3 include (+)-isokessane (93) by intramolecular attack of the alcohol (Scheme 26A). This compound has been isolated from Rubus rosifolius ([α]D0 = +19.2) and its structure was elucidated by one and two-dimensional NMR spectroscopy.[227] The alcohol 94 is known from guaiacwood oil[114] and can arise through a sequence of two 1,2-hydride shifts to Q3 and R4, followed by deprotonation. Alternatively, R4 can react by ring closure to (-)-10-epi-liguloxide (95) that has been isolated from Ligularia ([α]D0 = -3.5).[228] For this compound initially the structure of 96 (box in Scheme 26A) was assigned, but a later structural revision of liguloxide (98) showed the requirement of a structural revision also of 95,[229] because the two compounds are epimers as they are simultaneously formed by catalytic hydrogenation of 97 (Scheme 26B).[228]
4.5. Guaiols from cation K4

Guaiols from K4 are given in Scheme 27A. A direct ring closure explains the formation of (−)-kessane (99) that is known from the roots of several Japanese Valeriana species (kesso, [α]D = −7.2). Its structure including absolute configuration was established by correlation with known α-kessyl alcohol (103) that was converted into 99 by tosylation and treatment with LiAlH₄ (Scheme 27B), and by enantioselective synthesis from (+)-aromadendrene. Kessane (99) was later isolated again from Senecio, Bothriochloa intermedia, Prostanthera ovalifolia, Olearia phlogopappa and Machaerium multiflorum. Two sequential 1,2-hydride shifts via Q₄ to R₅ and ring closure give rise to (−)-liguloxide (100) from Ligularia ([α]D = −52.8). Initially, the structure of 101 was assigned to this compound, but elimination of water from 104 and catalytic hydrogenation yielded guaioxide (81) and liguloxide (100), showing that these compounds must be C₄ epimers (Scheme 27C). A 1,3-hydride shift from K₄ to R₆ and deprotonation lead to 102 that is observed in guaiacwood oil, while intramolecular attack of the alcohol to the cation in R₆ offers an explanation for the biosynthesis of 83 from Ligularia (Scheme 27A).

Scheme 26. A) Guaiols derived from K₃. B) Catalytic hydrogenation of 97 yields the epimers 95 and 98.

Scheme 27. A) Guaiols derived from K₄. B) Correlation of 103 with 99. C) Correlation of 104 with 81 and 100.

4.6. Cyclisation of hedycaryol by protonation at C10

The cyclisation of hedycaryol can also be initiated by protonation at C10 (Scheme 28), leading to the two enantiomeric series of cationic intermediates L₁–L₄ from (+)-1 and L₅–L₈ from (−)-1. Again, no examples of natural products for the series from (−)-1 with unambiguously determined absolute configuration are available, and thus the further discussion will be limited to the compounds derived from (+)-1.

It is interesting to note that subsequent hydride transfers in some cases lead to the same intermediates as discussed above (Scheme 29). Specifically, 1,2-hydride migrations from L₁–L₄ result in S₁–S₄ and then T₁–T₄. Herein, S₁ and T₁ are equal to R₃ and Q₂ (Scheme 25), while S₄ and T₄ are equal to R₄ and Q₃, respectively (Scheme 26). Compounds that were already discussed above and could have an alternative biosynthesis along these lines will not be presented here again. Furthermore, L₂ and L₃ can react in 1,3-hydride migrations to T₅ and T₆, respectively. Analogous steps are sterically not possible for L₁ and L₄, as was also shown by DFT calculations.
4.7. Guaiols potentially arising from hedycaryol by C10 protonation

Notably, most bicyclic 5–7 membered compounds from (+)-1 can be rationalised through a cyclisation induced by protonation at C4. While the biosynthesis in many cases has not been studied in detail and it is often unknown, whether compounds are formed from (+)-1 by C4 or C10 protonation, only two more compounds exist whose biosynthesis cannot be easily understood by C4 protonation (Scheme 30). In these cases C10 protonation could more reasonably explain their direct biosynthesis, which could lead to the only two remaining compounds (-)-1-epi-liguloxide (105) and (-)-bulnesoxide (106) that will be discussed here.

Starting from L2, a 1,2-hydride shift to S2 and intramolecular attack of the alcohol can give rise to (-)-105 ([α]_D = -25.6)\(^{238}\) while similar reactions from L3 via S3 can lead to (-)-106 ([α]_D = -8.2)\(^{239}\). In fact, both compounds were so far only obtained by synthesis\(^{238,239}\) which questions whether a protonation of (+)-1 at C10 in a terpene synthase catalysed reaction is relevant for any natural product, as it seems that the formation of all compounds that were isolated from natural sources can be explained through cyclisation of (+)-1 by C4 protonation and the subsequent reactions discussed above.

5. Conclusions

Many natural products are known that biosynthetically arise from hedycaryol (1). Plants generally make the compounds derived from (+)-1, while bacteria and fungi produce compounds derived from (-)-1, and because significantly more
research has been done on plants than on bacteria and fungi, most known compounds originate from (−)-1 and thus have 7R configuration. For many compounds, the absolute configurations have been secured by chemical correlations including total synthesis, but sometimes the situation is not fully resolved or even confusing. Particularly the assignments of optical rotations can be erroneous, which can easily happen if impure materials have been measured and the minor contaminants may have large optical rotations of opposite sign in comparison to the investigated compound. Especially the cases of the enantiomers 5-epi-10-epi-γ-eudesmol and 7-epi-γ-eudesmol that were both synthesised from the enantiomers of dihydrocarvone,[13,18] but then both reported to have negative optical rotations, and eventually of α-eudesmol for which the old work consistently reported a positive optical rotation, while new data support a negative value, deserve a revision.

Cyclisations of hedycaryol can either give a 6–6 membered bicyclic system, which represents the majority of cases. These cyclisations are always induced by protonation at C1, leading to a tertiary cationic intermediate, and not at C4 that would give a less stable and disfavoured secondary cation. Alternatively, a 5–7 membered bicyclic system can be formed for which protonations of C4 or C10 could potentially be relevant. As we demonstrated here, all compounds can be explained through protonation at C4, with only two remaining cases whose biosynthesis would need C10 protonation, but these compounds are only known as synthetic materials. Therefore, it seems that C4 protonation may serve as the general mechanistic model towards 5–7 bicyclic compounds, and we argue that this is because protonations at the C1–C10 double bond may preferentially happen at C1 to result in the 6–6 membered bicyclic systems. This reflects the situation that we have recently summarised for compounds derived from germacrene A for which the analysis of all known compounds also suggested that protonations of the C1–C10 double bond preferentially happen at C1 with formation of 6–6 membered bicyclic compounds, while protonations at the opposite C4–C5 double bond are directed toward C4 and induce formation of 5–7 membered bicyclic sesquiterpenes.[11] Taken together, hedycaryol and germacrene A show – not surprisingly – the same intrinsic reactivity, and the question of forming a 6–6 versus a 5–7 bicyclic ring system is a question of which of the two double bonds in the macrocycle becomes reprotonated. Notably, for patchoulol synthase different mechanisms with C4 and C10 protonation of germacrene A were discussed in the literature,[20–22] and a recent mechanistic study from our laboratories shows that C4 protonation is relevant for this molecule.[23] However, clearly more research is required to further confirm the general hypothesis outlined here, because for most compounds the biosynthesis has not been studied experimentally.

**Acknowledgements**

We thank Prof. Yoshinori Asakawa (Tokushima Bunri University) for fruitful discussions on the absolute configurations of eudesmols and their assigned optical rotations. Open Access funding enabled and organized by Projekt DEAL.

**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Keywords:** biosynthesis · configuration determination · hedycaryol · sesquiterpenes · structure elucidation

[1] J. Gershenzon, N. Dudareva, Nat. Chem. Biol. 2007, 3, 408–414.
[2] J. Degenhardt, T. G. Köllner, J. Gershenzon, Phytochemistry 2009, 70, 1621–1637.
[3] F. Chen, D. Tholl, J. Bohlmann, E. Pichersky, Plant J. 2011, 66, 212–229.
[4] A. Minami, T. Ozaki, C. Liu, H. Oikawa, Nat. Prod. Rep. 2018, 35, 1330–1346.
[5] J. S. Dickshat, Nat. Prod. Rep. 2016, 33, 87–110.
[6] M. B. Quin, C. M. Flynn, C. Schmidt-Dannert, Nat. Prod. Rep. 2014, 31, 94–147.
[7] X. Chen, T. G. Köllner, Q. Jia, A. Norris, B. Santhanam, P. Rabe, J. S. Dickshat, G. Shaulsly, J. Gershenzon, F. Chen, Proc. Natl. Acad. Sci. USA 2016, 113, 12132–12137.
[8] J. S. Dickshat, Angew. Chem. Int. Ed. 2019, 58, 15964–15976; Angew. Chem. 2019, 131, 16110–16123.
[9] H. Xu, J. S. Dickshat, Synthesis 2022, 54, 1551–1565.
[10] V. Harms, A. Kirschning, J. S. Dickshat, Nat. Prod. Rep. 2020, 37, 1080–1097.
[11] R. Chen, Q. Jia, X. Mu, B. Hu, X. Sun, Z. Deng, F. Chen, G. Bian, T. Liu, Proc. Natl. Acad. Sci. USA 2021, 118, e2023247118.
[12] V. J. J. Martin, D. J. Pitera, S. T. Withers, J. D. Newman, J. D. Keasling, Nat. Biotechnol. 2003, 21, 796–802.
[13] P. Baer, P. Rabe, K. Fischer, C. A. Citron, T. A. Klapcshinski, M. Groll, J. S. Dickshat, Angew. Chem. Int. Ed. 2014, 53, 7652–7666; Angew. Chem. 2014, 126, 7783–7787.
[14] Y.-H. Wang, H. Xu, J. Zou, X.-B. Chen, Y.-Q. Zhuang, W.-L. Liu, E. Celik, G.-D. Chen, D. Hu, H. Gao, R. Wu, P.-H. Sun, J. S. Dickshat, Nat. Catal. 2022, 5, 128–135.
[15] J. B. Hendrickson, Tetrahedron 1959, 7, 82–89.
[16] D. Arigoni, Pure Appl. Chem. 1975, 41, 219–245.
[17] H. Xu, J. S. Dickshat, Chem. Eur. J. 2020, 26, 17318–17341.
[18] H. Xu, B. Goldfuss, J. S. Dickshat, Chem. Eur. J. 2021, 27, 9758–9762.
[19] F. W. Semmler, F. Liao, Chem. Ber. 1916, 49, 794–798.
[20] V. Sykora, V. Herout, F. Sorn, Collect. Czech. Chem. Commun. 1955, 20, 220–226.
[21] R. O. Hellyer, Aust. J. Chem. 1962, 15, 157.
[22] R. V. H. Jones, M. D. Sutherland, Aust. J. Chem. 1968, 21, 2255–2264.
[23] R. V. H. Jones, M. D. Sutherland, J. Chem. Soc. Chem. Commun. 1968, 1229–1230.
[24] A. D. Waghe, S. K. Paknikar, S. C. Bhattacharyya, Tetrahedron 1964, 20, 2647–2654.
[25] T. G. Halsal, D. W. Theobald, K. B. Walshaw, J. Chem. Soc. 1964, 1029–1037.
[26] E. von Rudloff, Can. J. Chem. 1963, 41, 2876–2881.
[27] E. von Rudloff, F. M. Couchman, Can. J. Chem. 1964, 42, 1890–1895.
[28] Y. Fujise, I. Maruta, S. Ito, T. Nozoe, Chem. Pharm. Bull. 1964, 12, 991–994.
[29] G. L. K. Hunter, M. G. Moshonas, Anal. Chem. 1965, 37, 378–380.
[30] T.-S. Wu, H. Furukawa, Chem. Pharm. Bull. 1983, 31, 901–906.
[31] T.-S. Wu, Phytochemistry 1987, 26, 3094–3095.
[32] A. S. Bawdekar, G. R. Kelkar, S. C. Bhattacharyya, Tetrahedron 1967, 23, 1993–1996.
M. L. Maheshwari, T. C. Jain, R. B. Bates, S. C. Bhattacharyya, H. C. Barrett, G. Buechi, Y. Zhao, J. Yue, Z. Lin, J. Ding, H. Sun, I. Yosioka, Y. Sasaki, H. Hikino, S. K. Paknikar, C. G. Naik, A. F. Barrero, P. Arteaga, J. F. Quilez, I. Rodriguez, M. M. Herrador, M. L. Maheshwari, K. R. Varma, S. C. Bhattacharyya, D. F. MacSweeney, R. Ramage, R. Sattar, J. W. Huffman, C. A. Miller, A. R. Pinder, Chem. Eur. J. 2018, 24, 1919–1925.

Y. Zhao, J. Yue, Z. Lin, J. Ding, H. Sun, Phytochemistry 1997, 44, 459–464.

W.-M. Zhu, O. Zhao, S.-L. Li, X.-J. Hao, J. Asian Nat. Prod. Res. 2007, 9, 277–283.

R. P. T. Kim, V. Bihud, K. bin Mohamad, K. H. Leong, J. bin Mohamad, F. bin Ahmad, H. Hazni, N. Kasim, S. N. A. Halim, A. Wang, Molecules 2013, 18, 128–139.

I. A. Southwell, Tetrahedron Lett. 1977, 18, 873–876.

D. F. MacSweeney, R. Ramage, R. Sattar, Tetrahedron Lett. 1970, 11, 557–560.

B. Beagley, R. G. Pritchard, R. Ramage, I. A. Southwell, Acta Crystallogr. 1982, 38, 1319–1333.

A. F. Barrero, P. Arteaga, J. F. Quilez, I. Rodriguez, M. M. Herrador, J. Nat. Prod. 1997, 60, 1026–1030.

H. Itokawa, H. Morita, K. Watanabe, Chem. Pharm. Bull. 1987, 35, 1460–1463.

P. Shimojima, H. Kondo, S. Yuyu, T. Suzuki, H. Hagiwara, M. Ando, J. Nat. Prod. 1998, 61, 22–28.

S.-L. Li, L.-K. Ding, Acta Bot. Yunnan. 1993, 15, 303–305.

Y. Zhao, J. Yue, Z. Lin, J. Ding, H. Sun, Phytochemistry 1997, 44, 459–464.

W.-M. Zhu, O. Zhao, S.-L. Li, X.-J. Hao, J. Asian Nat. Prod. Res. 2007, 9, 277–283.

R. P. T. Kim, V. Bihud, K. bin Mohamad, K. H. Leong, J. bin Mohamad, F. bin Ahmad, H. Hazni, N. Kasim, S. N. A. Halim, A. Wang, Molecules 2013, 18, 128–139.

I. A. Southwell, Tetrahedron Lett. 1977, 18, 873–876.

D. F. MacSweeney, R. Ramage, R. Sattar, Tetrahedron Lett. 1970, 11, 557–560.

B. Beagley, R. G. Pritchard, R. Ramage, I. A. Southwell, Acta Crystallogr. 1982, 38, 1319–1333.

A. F. Barrero, P. Arteaga, J. F. Quilez, I. Rodriguez, M. M. Herrador, J. Nat. Prod. 1997, 60, 1026–1030.

H. Itokawa, H. Morita, K. Watanabe, Chem. Pharm. Bull. 1987, 35, 1460–1463.

P. Shimojima, H. Kondo, S. Yuyu, T. Suzuki, H. Hagiwara, M. Ando, J. Nat. Prod. 1998, 61, 22–28.

S.-L. Li, L.-K. Ding, Acta Bot. Yunnan. 1993, 15, 303–305.

Y. Zhao, J. Yue, Z. Lin, J. Ding, H. Sun, Phytochemistry 1997, 44, 459–464.

W.-M. Zhu, O. Zhao, S.-L. Li, X.-J. Hao, J. Asian Nat. Prod. Res. 2007, 9, 277–283.

R. P. T. Kim, V. Bihud, K. bin Mohamad, K. H. Leong, J. bin Mohamad, F. bin Ahmad, H. Hazni, N. Kasim, S. N. A. Halim, A. Wang, Molecules 2013, 18, 128–139.

I. A. Southwell, Tetrahedron Lett. 1977, 18, 873–876.
