Recent advances in the chemistry of caryophyllene

Isidro G. Collado,[a] James R. Hanson[b] and Antonio J. Macías-Sánchez[a]

[a]*Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Cádiz, Apartado 40, 11510, Puerto Real, Cádiz, Spain*
[b]*The School of Chemistry, Physics and Environmental Science, University of Sussex, Brighton, Sussex, UK BN1 9QJ*

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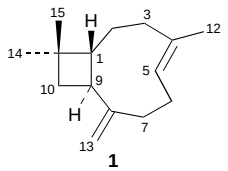
1 Introduction

(−)-*trans*-Caryophyllene [(−)β-caryophyllene] **1** plays an important role in the chemistry of the sesquiterpenoids. Caryophyllene **1** and its hydroxylation products are found in many plants and fungi.[1] The most abundant source of caryophyllene **1** is the clove tree *Eugenia caryophyllata* (*Syzygium caromaticum*). Caryophyllene **1** is a biogenetic relative of humulene **2**,[2] with which it cooccurs. The unusual structure of caryophyllene involving a cyclobutane ring fused in a *trans* manner to a nine-membered ring containing a 1,5-diene, provides the basis for a variety of transformations leading to tricyclic sesquiterpenoids.[3] An understanding of the chemistry and conformational aspects of these cyclizations is important in rationalizing the biosynthesis of these families of polycyclic sesquiterpenes. Since caryophyllene **1** is readily available, these cyclizations may provide useful access to rarer sesquiterpenoids in sufficient quantities for the chemical and microbiological synthesis of biologically interesting sesquiterpenoids. The object of this review is to describe recent advances in the chemistry of caryophyllene **1** in the light of its conformational mobility and cyclizations.



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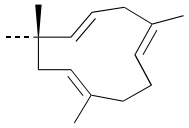
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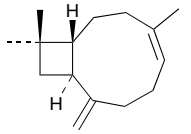
Caryophyllene **1** has been known since 1834, although the material obtained in the initial studies on oil of cloves was a mixture of *cis*-caryophyllene **3** and *trans*-caryophyllene **1** with humulene **2**. In 1892, Wallach and Walker[4] obtained its crystalline nitrosite (1,2-nitro-nitroso derivative) and were able to characterize *trans*-caryophyllene **1**. Extensive degradative studies over the following 60 years led to the structure of caryophyllene. Oxidative degradation of caryophyllene afforded three cyclobutane dicarboxylic acids, norcaryophyllenic acid **4**, caryophyllenic acid **5** and homocaryophyllenic acid **6**, which have been synthesized,[5] thus establishing the presence of the four-membered ring. The nature of the second ring was a matter of doubt for some years but it was eventually clarified by the degradation of caryophyllene oxide.[6] This led to the realization that caryophyllene possessed a nine-membered ring. Studies on the acid-catalysed cyclization of caryophyllene and caryophyllene oxide[7,8] revealed the formation of two series of cyclization products possessing the caryolane and clovane skeleta and exemplified by the alcohol caryolan-1-ol **7a** and the unsaturated hydrocarbon clov-2-ene **8**. The elucidation of the structures of these cyclization



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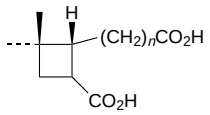
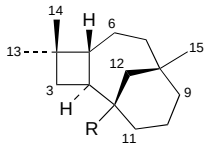
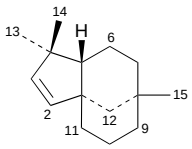


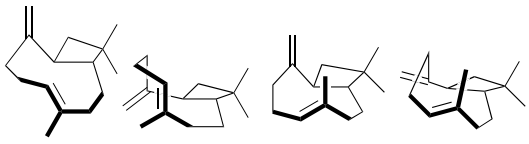
4 *n* = 0
5 *n* = 1
6 *n* = 2



7a R = OH
7b R = Cl

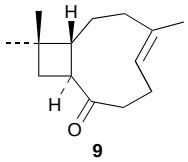


8a



Δ***H***				
(Kcal mol^{-1})	12.94	14.78	13.69	16.94
% (MM1)	75.33	3.37	21.22	0.09
% (^{13}C NMR)	75	–	25	–

Scheme 1



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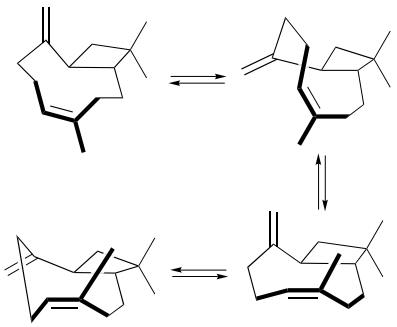
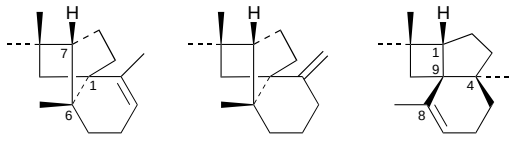
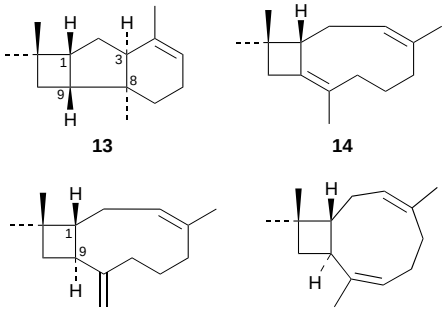


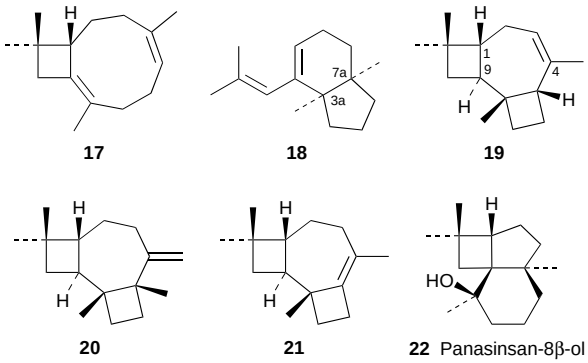
Scheme 2



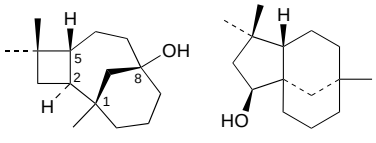
10 α-Neoclovene **11** β-Neoclovene **12** α-Panasinsene



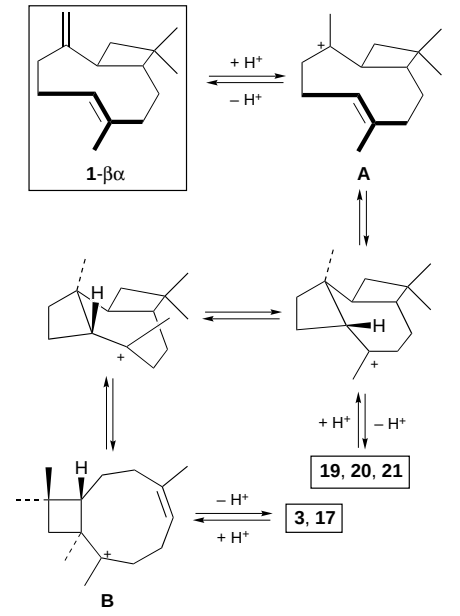
13 **14** **15** **16**



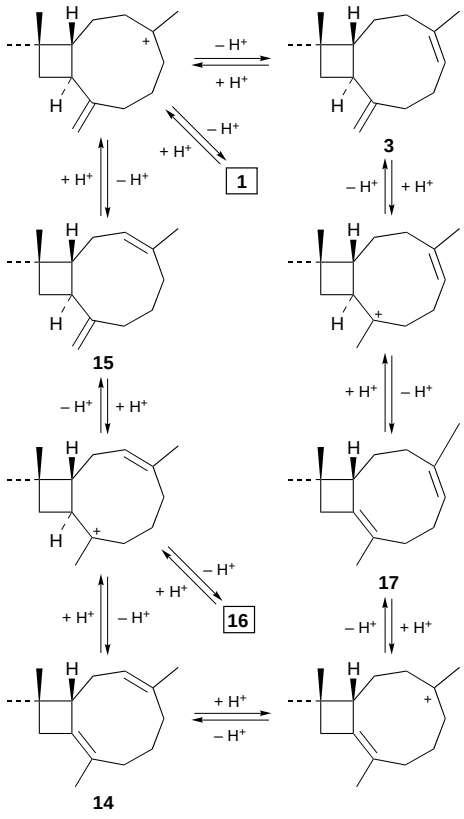
17 **18** **19** **20** **21** **22** Panasinsan-8β-ol



23 Isocaryolan-8-ol **24** Clovan-2β-ol



Scheme 3



Scheme 4

products in 1953,[9] together with an X-ray structure of caryolanyl chloride **7b**[10] and studies on the absolute stereochemistry of these alcohols,[11] led to the establishment of the complete stereochemistry of (−)-*trans*-caryophyllene **1** and its *cis* isomer, called isocaryophyllene **3**. This work has been summarized in previous reviews.[12]

Two general features emerged from this earlier work. The first was that the endocyclic 4,5-double bond of *trans*-caryophyllene **1** was more reactive than the exocyclic 8(13)-double bond and the second was the propensity of the system to undergo cyclization reactions.

The first synthesis of *trans*-caryophyllene **1** and isocaryophyllene **3** was reported in 1963[13] and a number of other successful syntheses have subsequently been reported.[14–19]

2 The conformations of caryophyllene

Molecular mechanics calculations and ^{13}C NMR[20,21] studies have shown that there are four possible conformations of (−)-*trans*-caryophyllene **1** distinguished by the relative

Table 1 Major cyclization products of caryophyllene with different reagents

Starting material	Product	Reagent(s)	Refs.
1	**7**	Chloroacetic acids (mono-, di- and tri-)	36,37
		AcOH–cationic exchange resins	38
1	**8**	Lewis acids (*e.g.* $AlCl_3$)	39
		AcOH–cationic exchange resins	38
1	**26**	Synthetic zeolites	40
1	**27**	Chloroacetic acids (mono-, di- and tri-)	36,37
		AcOH–cationic exchange resins	38
1	**28**	HCO_2H	41,42
1	**29**	Chloroacetic acids (mono-, di- and tri-)	36,37
		AcOH–cationic exchange resins	38
		Synthetic zeolites	40
1	**30**	Chloroacetic acids (mono-, di- and tri-)	36,37
1	**31**	Lewis acids (*e.g.* $AlCl_3$)	39
1	**33**[a]	HCO_2H	41,42
1	**32**	$ClSO_2N=C=O$[b]	43

[a]Compound **33** = caryolan-1-yl formate, [b]chlorosulfonyl isocyanate.

Table 2 Examples of natural products related to caryophyllene cyclization products

Source	Compound(s)	Refs.
Panax ginseng	α-Panasinsene **12**	44
	β-Panasinsene **34**	
	α-Neoclovene **10**	
	β-Neoclovene **11**	
	Panasinsanol A **35**	
	Panasinsanol B **22**	
Naematoloma fasciculare	Naematolin C **36**	45
	Naematolin G **37**	
Dipterocarpus pilosus	Clov-2β-9α-diol **38**	66
Magnolia ovobata	Clovanemagnolol **39**	46
	Caryolanemagnolol **40**	
Collybia confluens	Collybial **41**	47
Panax ginseng	Ginsenol **42**	109
Oil of hops and cloves	Triphyllenol **43**	74

disposition of the exocyclic methylene and olefinic methyl groups. The predicted and experimentally determined populations of these conformations are shown (Scheme 1). NMR spectroscopic studies indicate that there is a low inversion barrier ($\Delta G^1 = 16.25 \pm 0.11$ or 16.1 ± 0.3 kcal mol^{-1}) between the βα- and ββ-conformers. The relative population of these conformers is reflected to a certain extent in the ratios of products of various reactions of caryophyllene such as epoxidation, hydroboration and photooxidation.[20] A similar ratio of conformers (80:20) has been found for the nor-ketone **9**.[22]

The conformers of the *cis* isomer, isocaryophyllene **3** (Scheme 2), differ far less in their stability[23,24] and there is a lower inversion barrier between them.[25]

3 Cyclization reactions of *trans*-caryophyllene

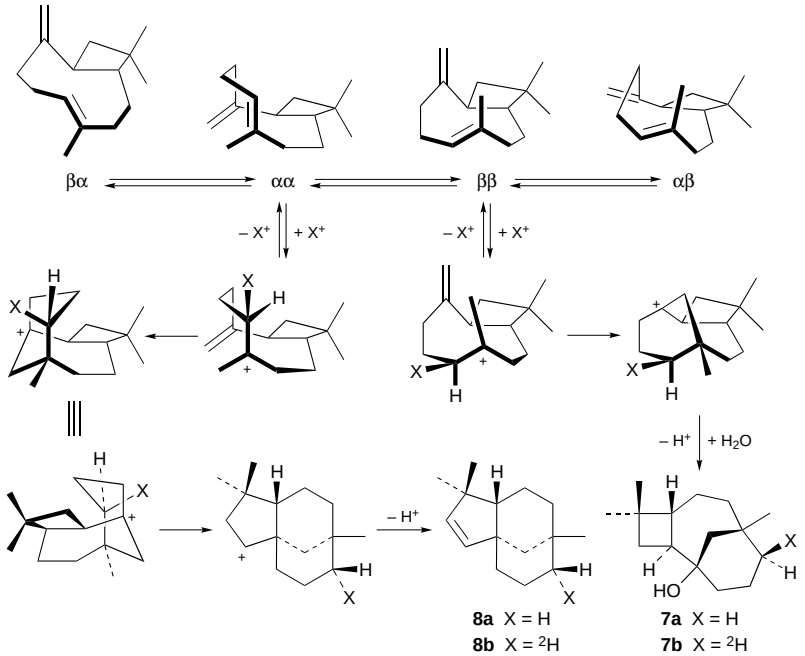
The cyclizations of *trans*-caryophyllene **1**, initiated by electrophilic attack on one of the two double bonds may be considered under three headings: (i) cyclizations in acidic media such as sulfuric acid–diethyl ether; (ii) mercuration and reductive demercuration with sodium borohydride; and (iii) reactions in super-acid media.

3.1 Cyclizations in acidic media

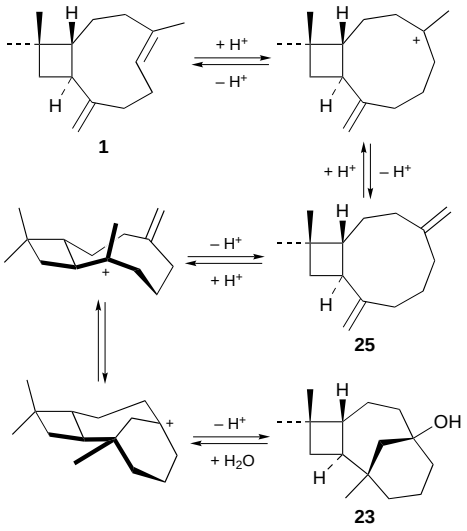
When *trans*-caryophyllene **1** is treated with three equivalents of concentrated sulfuric acid in diethyl ether at 0–20 °C for 30 min, a mixture containing at least 14 hydrocarbons and 4 alcohols is formed. After three days this mixture is simplified to 3 hydrocarbons and 3 alcohols. The products that are formed after 30 min are: clov-2-ene **8a**,[9] caryolan-1-ol **7a**,[9] α-neoclovene **10**,[26] β-neoclovene **11**,[26] α-panasinsene **12**,[27] **13**,[28] isocaryophyllene **3**,[9,29] **14**,[30] **15**,[30] **16**,[30] **17**,[3b] **18**,[3b] **19**,[3b] **20**,[3b] **21**,[3b] panasinsan-8β-ol (panasinsanol B) **22**,[3b] isocaryolan-8-ol **23**[31] and clovan-2β-ol **24**[32].

The major products that are found after three days are caryolan-1-ol **7a**, clov-2-ene **8a** and α-neoclovene **10**.

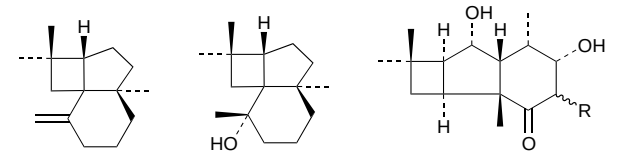
Protonation of the exocyclic double bond of the major βα-conformer of **1**, generates the carbocation **A** which has the correct geometry to cyclize, with the formation of **19**, **20** and

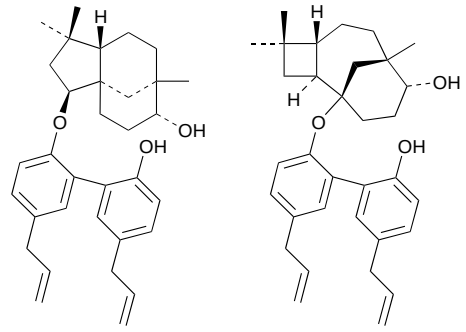


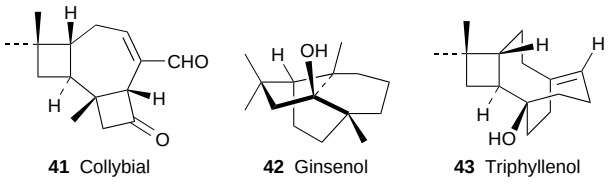
Scheme 5

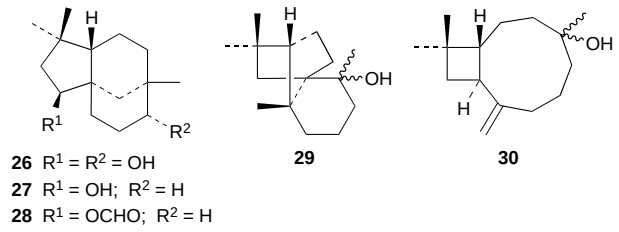


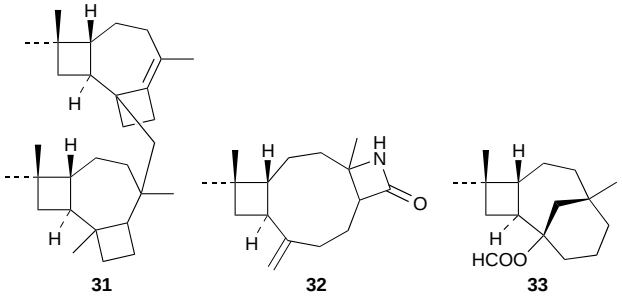
Scheme 6







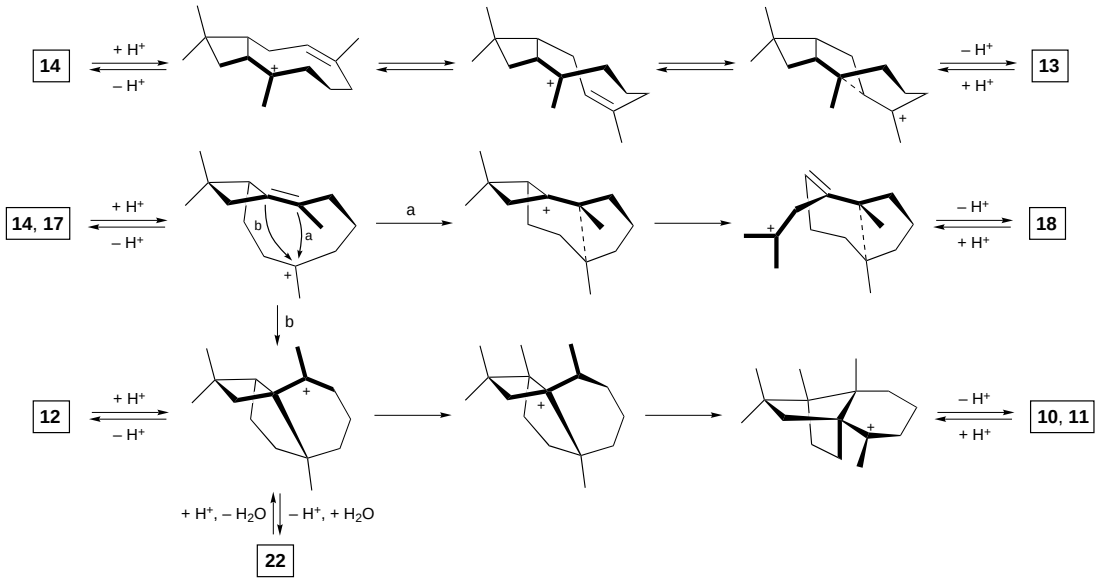




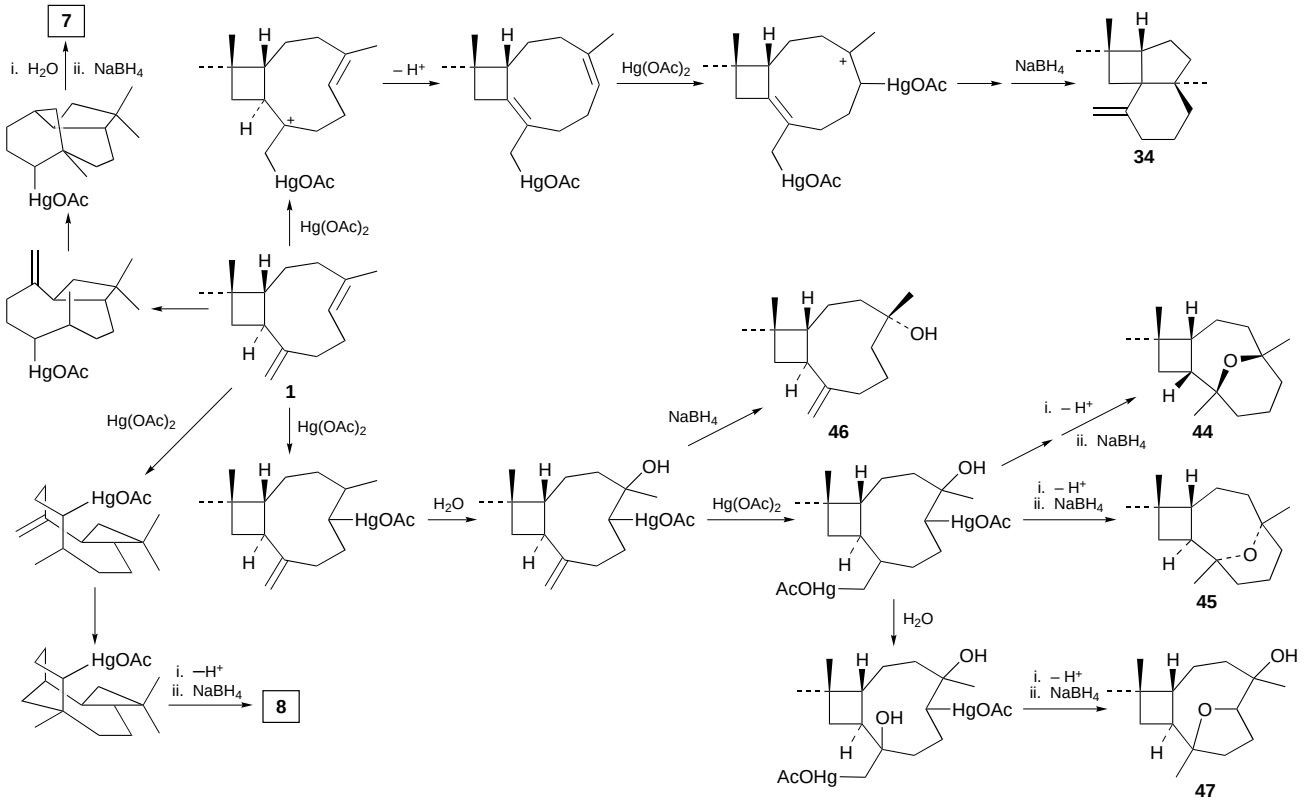
21 (Scheme 3). Alternatively the isocaryophyllene carbocation **B** may be formed and undergo further elimination to form the isocaryophyllene series.

These cyclizations and rearrangements are reversible and eventually lead to the more stable isomers. Protonation of the endocyclic double bond and elimination leads to a further series of isomers **14–17** (Scheme 4). These alkenes may also be obtained by dehydrochlorination ($AgNO_3$–DMSO) of *trans*-caryophyllene **1** or isocaryophyllene dihydrochloride.[33]

The different tricyclic skeleta that are formed, reflect the major conformers that are present (Scheme 5). The αα-conformer undergoes a cyclization on the lower face of the molecule generating the clovane skeleton, after expansion of the four-membered ring. When the ββ-conformer is involved,



Scheme 7



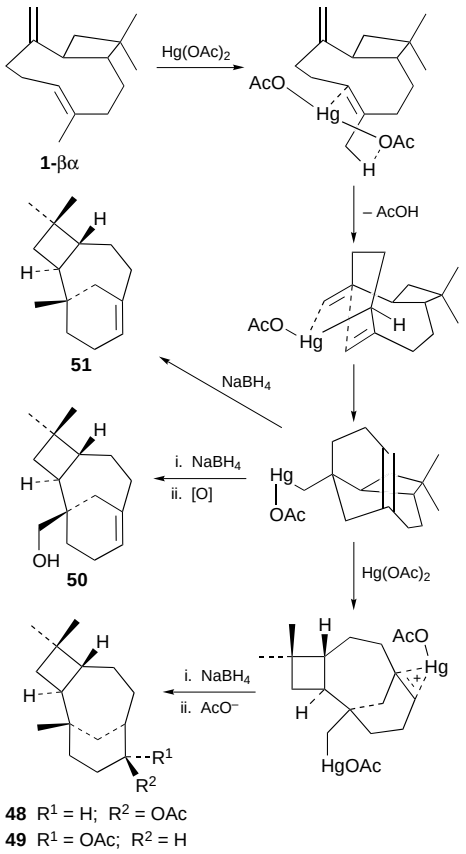
Scheme 8

cyclization takes place on the β-face of the molecule, to yield caryolan-1-ol **7a**. These cyclizations have been carried out in deuteriated sulfuric acid to afford [9β-^{2}H]caryolan-1-ol **7b** and [9α-^{2}H]clov-2-ene **8b**.[34] The differing stereochemistry of the deuterium confirms that these compounds originate from the different conformations of *trans*-caryophyllene **1**.

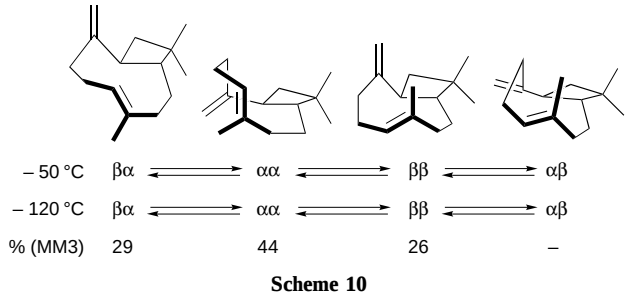
The isocaryolan-8-ol **23** may be formed *via* the isomerization of the endocyclic alkene to an exocyclic position. Protonation of the 8(13)-alkene **25** and cyclization affords **23** (Scheme 6). This compound has been formed by the reaction of **1** on acidic alumina,[35] whilst the exocyclic alkene has been obtained through the hydrochlorination–dehydrochlorination of trans-caryophyllene **1**.[30]

The formation of double bond isomers of *trans*-caryophyllene **1**, particularly **14** and **17**, and their subsequent cyclization, may generate the neoclovane skeleton (compounds **10** and **11**), the panasinsane skeleton (compounds **12** and **22**) and the compounds **13** and **18** (Scheme 7).

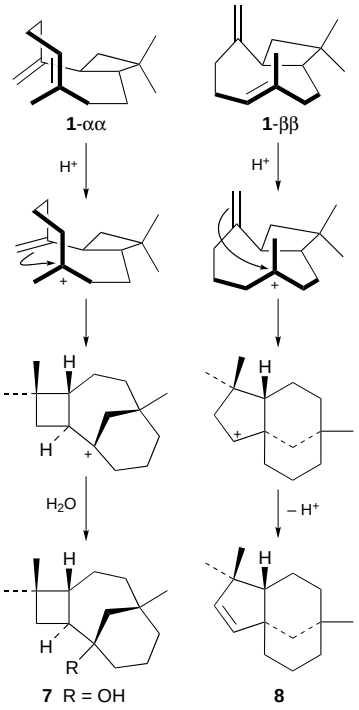
The formation of some of these compounds is favored by other acidic media. These are listed in Table 1. Some related natural products are listed in Table 2. The dimeric structure **21**, obtained by heating *trans*-caryophyllene **1** in toluene at 120 °C in the presence of Lewis catalyst is interesting in that it represents a trapped form of one of the initial cyclization products of caryophyllene prior to their rearrangement and thus provides evidence for the formation of such carbocations.



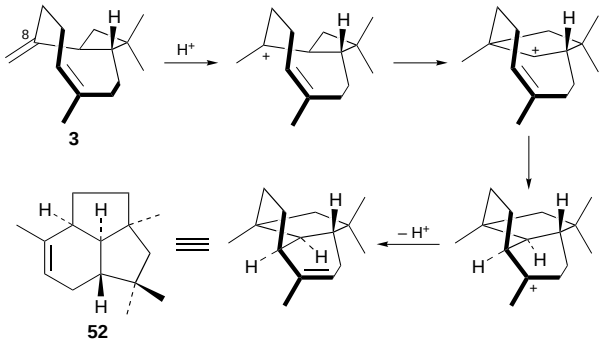
Scheme 9



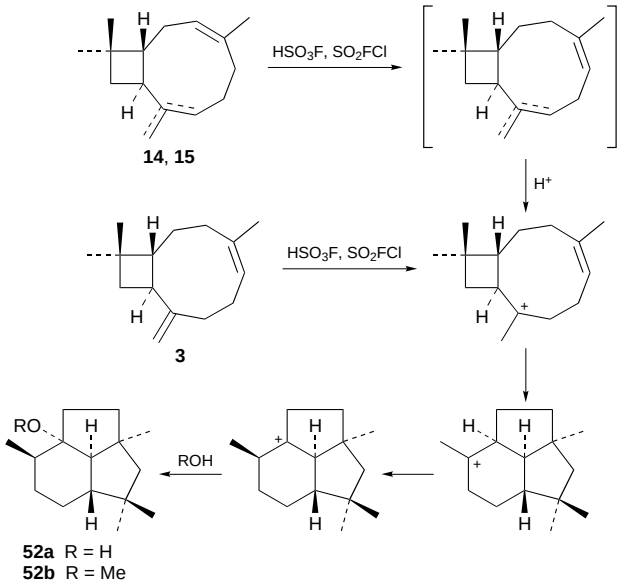
Scheme 10



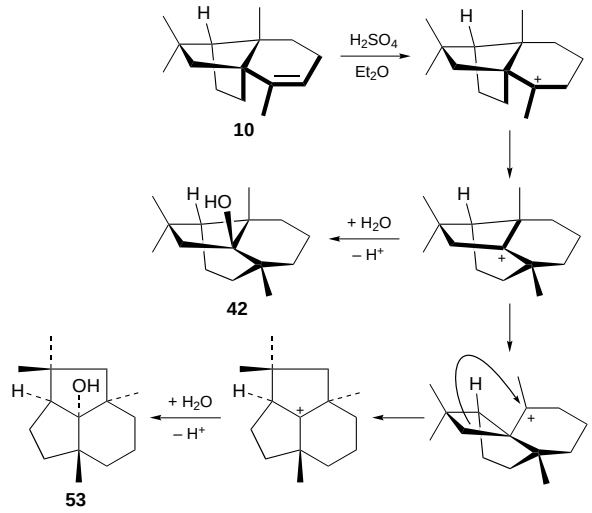
Scheme 11



Scheme 12



Scheme 13



Scheme 14

3.2 Mercuration–demercuration

The mercuration–reductive demercuration reaction in THF gives three series of compounds:[48] (i) a non-polar fraction comprising β-panasinsene[49] **34** and clov-2-ene **8**; (ii) an oxide fraction comprising the epimeric caryophyllene-4,8-oxides **44** and **45**, and (iii) a more polar fraction comprising caryolan-1-ol **7** and the caryophyllen-4-ols **46** and **47** (Scheme 8).

When the mercuration takes place in acetic acid, the products have the 1,4,4-trimethyltricyclo-12α-methylen[6,3,1,$0^{2,5}$] dodecane skeleton (compounds **48**–**51**) (Scheme 9).[50] The generation of this, including the formation of the anti-Bredt alkenes **50** and **51**, may arise through a transannular migration of the mercuric acetate in the course of the cyclization.

3.3 Cyclizations in super-acid media

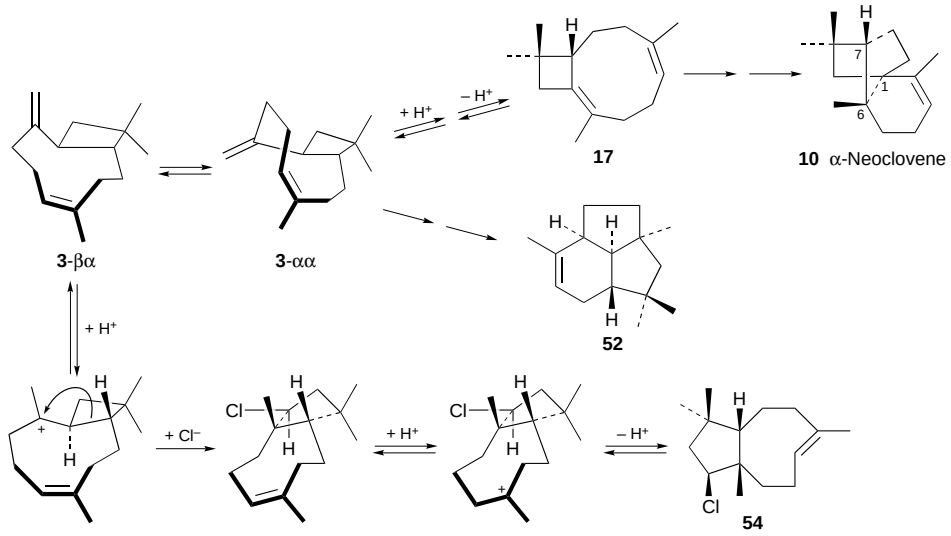
The distribution of the products obtained from the rearrangement of *trans*-caryophyllene **1** in a super-acid medium differs considerably from that obtained in normal acidic media. At the temperatures used for super-acid cyclization the various conformers of caryophyllene **1** are not rapidly interconverting.

Examination of the low temperature (− 124 °C) ^{13}C NMR spectrum of *trans*-caryophyllene **1** in SO_2FCl provided evidence for a significant transition barrier between the ββ- and αα-conformations.[25] These studies provide experimental support for the results of population predictions based on MM3[51] calculations, suggesting proportions of 44, 29 and 26% for αα-, αβ- and ββ-conformations, respectively (Scheme 10. Scheme 1 for MM1 predictions).[3b]

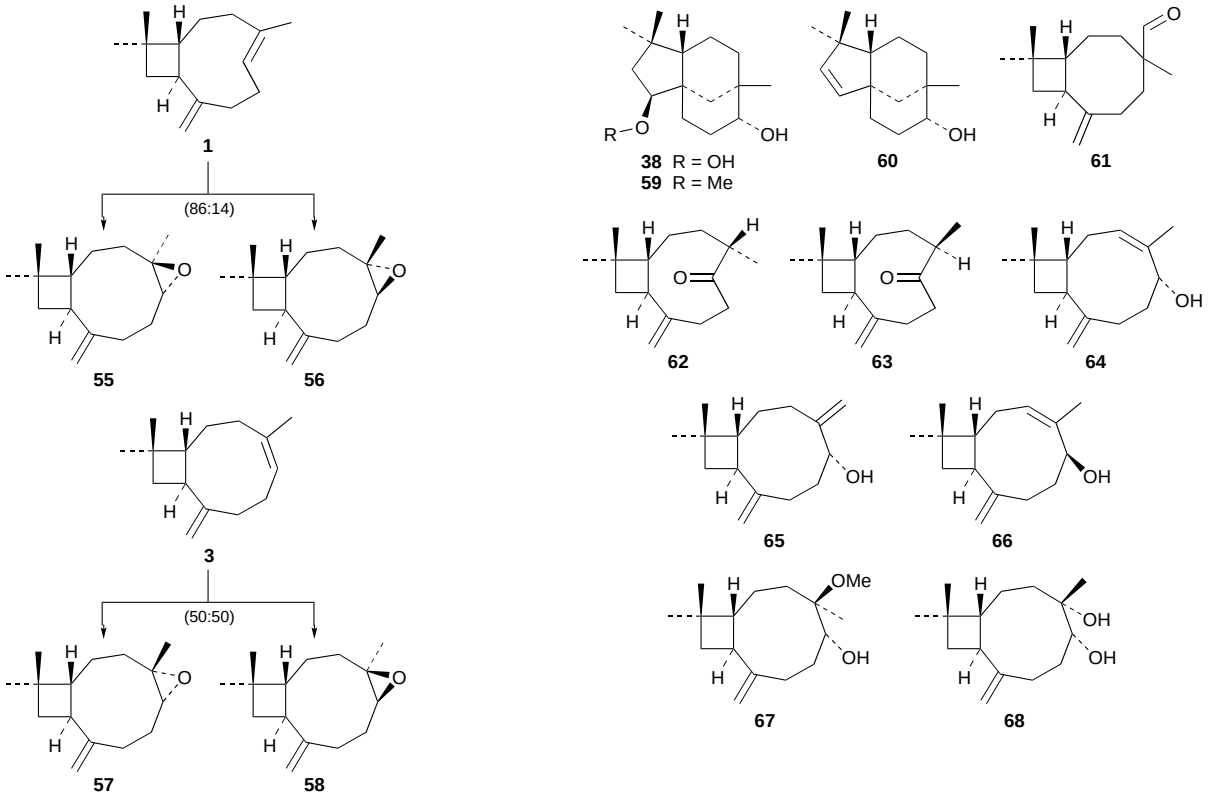
The implication of this is that in the absence of interconversion between the conformers that give rise to caryolan-1-ol **7** and clovene **8**, the cyclization products obtained from *trans*-caryophyllene **1** in super-acid medium are the sum of the products obtained separately from **7** and **8** (Scheme 11). These are discussed later under the cyclization of **7** and **8**.

4 Isocaryophyllene

Although there have not been extensive studies on the acid-catalysed cyclization of isocaryophyllene **3**, the principal products are known. When isocaryophyllene was treated with concentrated sulfuric acid in diethyl ether at 0 °C, α-neoclovene **10** and **52** were obtained.[28b,52] The latter, which had not been detected in the cyclization of *trans*-caryophyllene **1**, may be formed as in Scheme 12. It is the 11-epimer of the



Scheme 15



Scheme 16

botrylane sesquiterpenoids, formed by the fungus *Botrytis cinerea*.[53]

The transformations which the other double-bond isomers of *trans*-caryophyllene **1** undergo, have been described previously but their behavior in super-acid medium is again different and can be summarized in Scheme 13. Interestingly they also afford the 11-epibotrylane skeleta.[54]

Recently, the acid-catalysed cyclization of isocaryophyllene **3** has been reexamined.[55] In addition to the known compounds caryolan-1-ol **7**, α-neoclovene **10** and **52**, the compounds ginsenol **42** and **53** were obtained. Ginsenol **42** is the alcohol derived from a carbocation proposed in the formation of α-neoclovene **10** from *trans*-caryophyllene **1** (Scheme 7). Ginsenol is also a natural product, isolated from *Panax ginseng*.[109] Compound **53** originates from further rearrangement of α-neoclovene **10** (Scheme 14).

Treatment of isocaryophyllene **3** with SiO_2–$FeCl_3$[55] yielded compounds **10**, **52**, **42**, **53** and a bicyclic chloro-derivative **54** (Scheme 15). The structure this compound has been confirmed by synthesis.[55]

5 Caryophyllene oxides

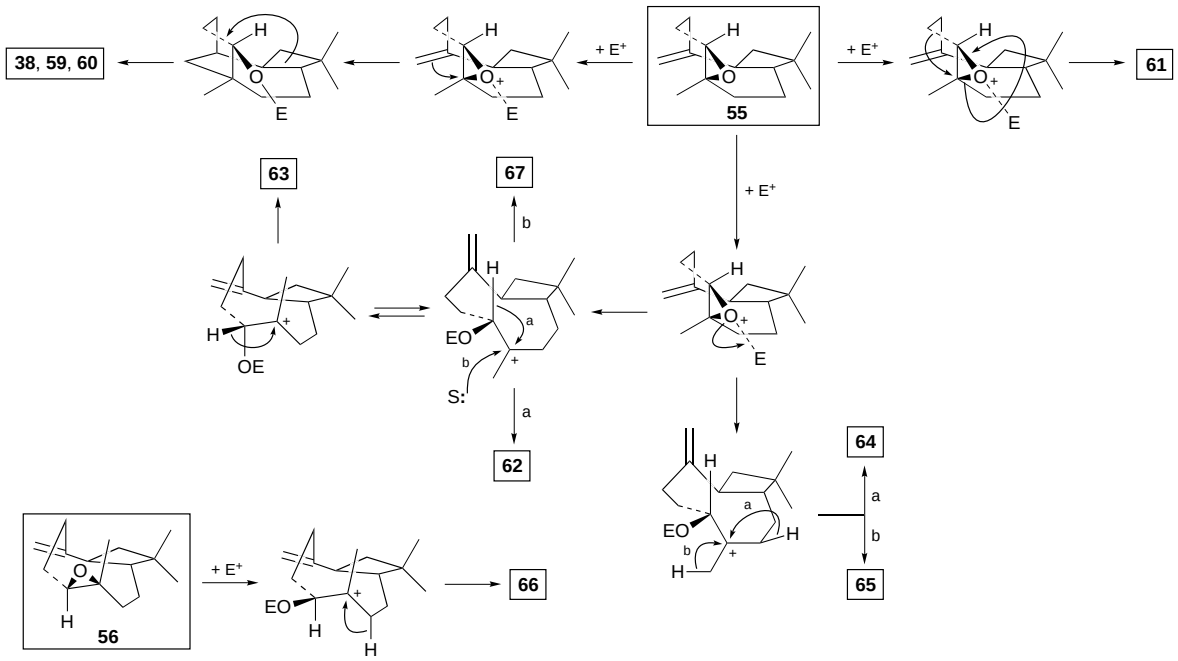
trans-Caryophyllene **1** and isocaryophyllene **3** may be epoxidized to form the epimeric endocyclic epoxides (Scheme 16):[56] (*a*) 4β,5α-epoxycaryophyll-8(13)-ene **55** and 4α,5β-epoxycaryophyll-8(13)-ene **56**, from **1**; (*b*) 4α,5α-epoxycaryophyll-8(13)-ene **57** and 4β,5β-epoxy-caryophyll-8(13)-ene **58** from **3**.

The proportions of these epoxides reflect the conformational composition of **1** and **3**.[56] The most abundant of these epoxides **55** occurs naturally in oil of cloves and is commercially available as caryophyllene oxide **55**.

Table 3 Major cyclization products of caryophyllene oxides with different reagents

Starting material	Final product	Reagent(s)	Refs.	Starting material	Final product	Reagent(s)	Refs.
55	**38**	H_2SO_4–Et_2O	57	**55**	**63**	Synthetic zeolites	65
		AcOH–AcONa (pH 4 buffer)	59	**55**	**64**	Solid acids[a]	61
55	**60**	BF_3–Et_2O	60			AcOH–AcONa (pH 4 buffer)	59
		Solid acids[a]	61			Activated alumina	64,66
		Synthetic zeolites	62			Pyridine – HBr	67
55	**61**	BF_3–Et_2O	60	**55**	**65**	Solid acids[a]	61
		Gas chromatography	63			Activated alumina	64
		AcOH–AcONa (pH 4 buffer)	59			AcOH–AcONa (pH 4 buffer)	59
55	**62**	BF_3–Et_2O	60	**55**	**68**	AcOH–AcONa (pH 4 buffer)	59
		Activated alumina	64	**56**	**66**	Solid acids[a]	61
		Solid acids[a]	61			Activated alumina	66
		Synthetic zeolites	62,65				
		AcOH–AcONa (pH 4 buffer)	59				

[a]Lewis acids, *e.g.* supported on silica or alumina.



Scheme 17

5.1 Cyclization in an acidic medium

The major acid-catalysed (sulfuric acid–diethyl ether) cyclization product of caryophyllene oxide **55** is clovan-2β,9α-ol **38**.[57,58] Its formation is analogous to that of clovene **8** from *trans*-caryophyllene **1**. Other products **59–68** which have been obtained with different reagents are given in Table 3. Their formation may be rationalized as shown in Scheme 17.

Cyclization of 4β,5α-epoxycaryophyll-8(13)-ene **55** with the mild π-acid catalyst tetracyanoethylene (TCNE) in methanol, gave 2β-methoxyclovan-9α-ol **59**, together with the products of simple methanolysis, 4β-methoxycaryophyllen-5α-ol **67**, and elimination, **64**. However, in dipolar aprotic solvents, elimination products were formed.[68]

5.2 Mercuration–demercuration

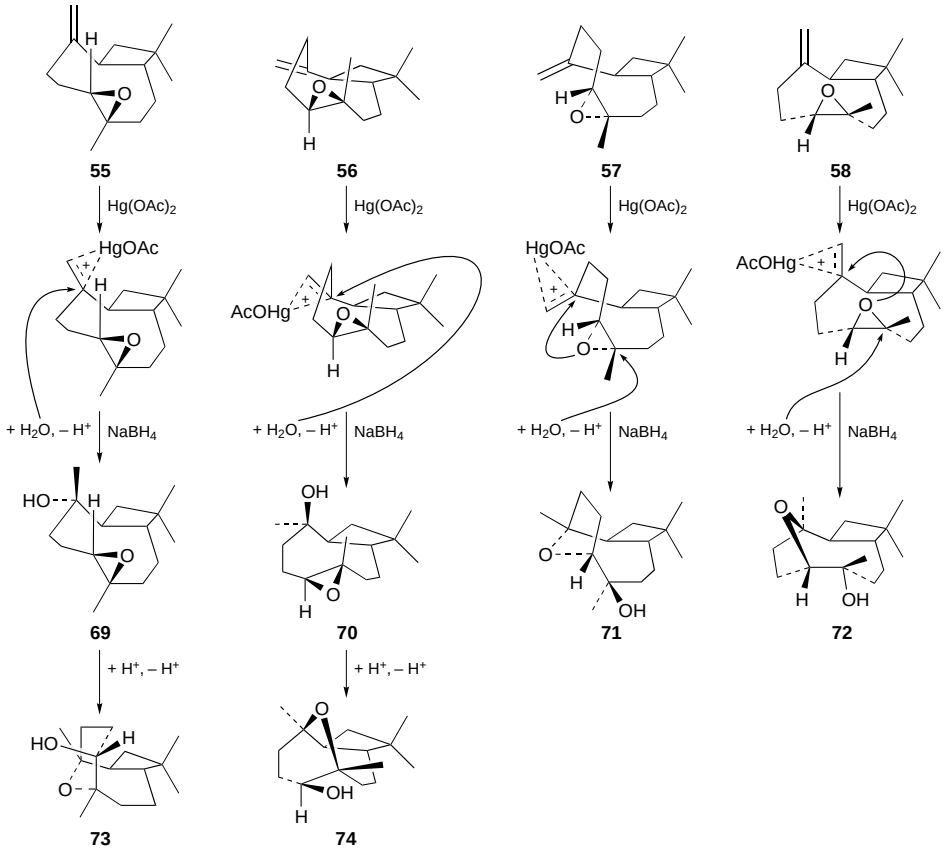
The cyclic ethers that are obtained by reaction with mercuric acetate in aqueous tetrahydrofuran[69] reflect the relative disposition of the exocyclic alkene and the 4,5-epoxide (Scheme 18). In the epoxides derived from isocaryophyllene **3**, the 4,5-epoxide may behave as an internal nucleophile forming the ether bridge. On the other hand, in the epoxides derived from *trans*-caryophyllene **1**, hydration of the mercuric acetate adduct leads to a C-8 tertiary alcohol which then attacks the epoxide with the formation of the cyclic ethers **73** and **74**.

When the reaction is performed in acetic acid,[70] the major product is β-panasinsen-5α-ol **75** (Scheme 19). This may be formed *via* an allylic organomercurial derivative. The acetic acid medium favors elimination rather than hydration to discharge the initial carbocation.

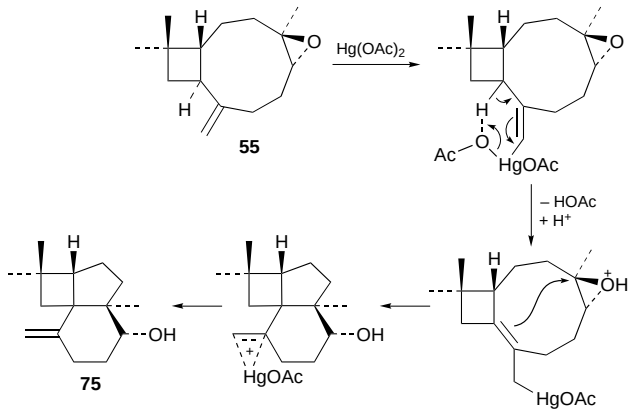
5.3 Cyclization in a super-acid medium

The products of the reaction of the epoxides of isocaryophyllene **3**, with super-acid (HSO_3F–SO_2FCl),[71] which are compounds **57** and **58**, are determined by the stereochemistry at C-4. Rear side attack by the exocyclic double bond takes place on the α-face of **58** and the β-face of **57**. This leads to the enantiomeric ions **A** and **B** and thence to the enantiomeric dienols **77** and **79** (Scheme 20). Under conventional acidic conditions, a clovane **78** and a caryolane **76** derivative are formed.

The products from caryophyllene oxide **55** are temperature dependent (Scheme 21). At −100 °C clov-2-en-9α-ol **60** is



Scheme 18



Scheme 19

formed, but at − 80 °C methyl group migration and dehydrogenation takes place. Compound **81**, with the selinane skeleton, has been isolated when the reaction was carried out at − 130 °C. It is possible that this was formed *via* a humulene carbocation (Scheme 22).

6 Solvolytic reaction of caryophyllenols

Solvolysis of the methanesulfonate **82** derived *via* caryophyllene oxide, afforded compounds with the triphyllane skeleton (compounds **43**, **83**–**85**).[72,73] The parent alcohol **43** is a natural product that is found in cloves and hops.[74] Although the methanesulfonate **82** can exist in four different conformations, only one of these **82α** has the appropriate geometry for cyclization (Scheme 23).

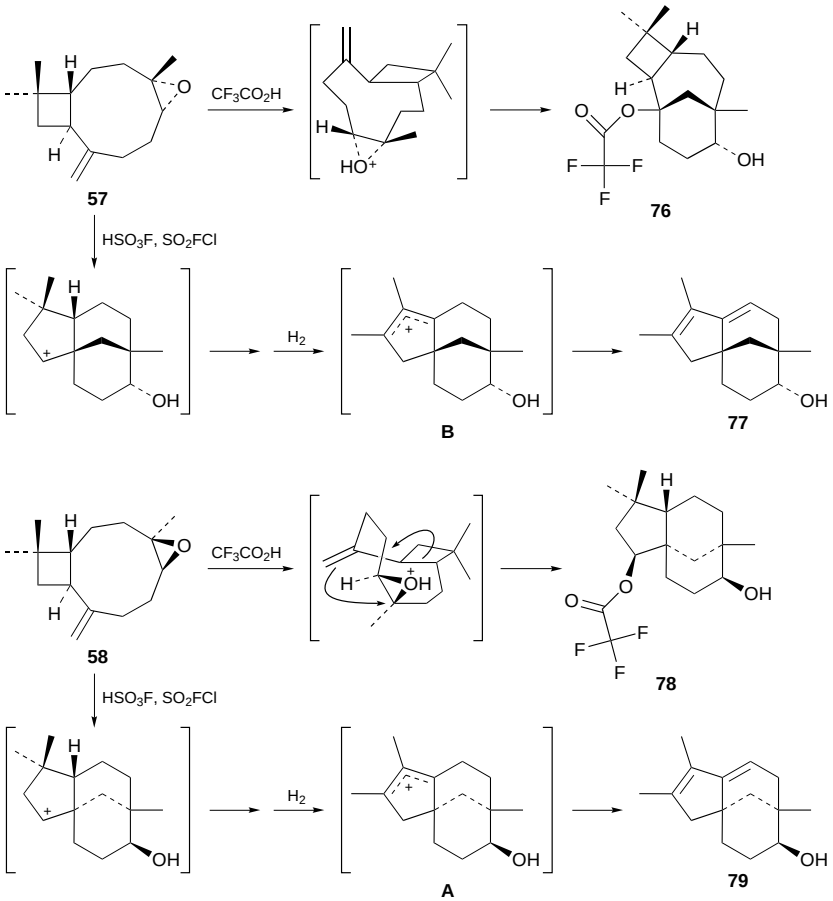
When the epimeric allylic acetates **86** and **89**, prepared from the epoxides **55** and **58**, respectively, were cyclized by oxymercuration and reduction, the isocaryolanes **87** and **90** were obtained (Scheme 24).[50]

A reinvestigation of the reaction of caryophyllene oxide **55** with H_2SO_4–Et_2O[75] led to the isolation of two ethers, **91** and **92**, derived from further reaction on the exocyclic double bond of the isomerization and epoxide opening products, **64** and **88**, respectively. Compound **91** was also obtained in the treatment of caryophyllene oxide **55** with TCNE. Compounds **93**–**95** were also obtained from further reaction on the exocyclic double bond of the caryophyllenols **64** and **65**.[68,76]

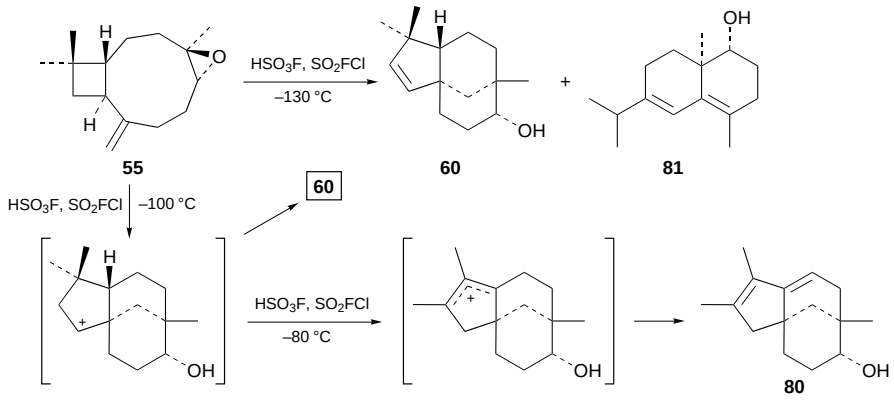
Sharpless *syn* epoxidation of allylic alcohols **64**, **65** and **66** led to the formation of the *trans* epoxy alcohols **96**–**98**.[77] The products of the reaction of the epoxy alcohols with TCNE reflected the stereochemistry of the parent epoxide. The 3α,4α-epoxide **96** gave the 1-methoxycaryolan-7α,9β-diol **99**, whilst the 3β,4β-epoxide **97** gave the simple methanolysis product **100**. On the other hand, the 4β,12-epoxide **98** afforded 2β-methoxyclovan-9α,15-diol **101** accompanied by (4*R*)-12-hydroxy-5-oxocaryophyll-8(13)-ene **102** (Scheme 26). Formation of *trans* epoxides by *syn* epoxidation is a consequence of the conformational flexibility of the nine-membered ring, which places the alcohol at C-5 close to the α-face of the *endo*-alkene in **96** and close to the β-face in **97** and **98**. The epoxy alcohol **96** has also been isolated from an extract of *Sindora sumatrana*.[78]

7 Thermal rearrangements of *trans*-caryophyllene

Pyrolysis of caryophyllene at low pressure afforded isocaryophyllene **3** by a series of [3,3]-sigmatropic rearrangements of the 1,5-diene[79] (Scheme 27). When this Cope rearrangement was blocked through epoxidation, a reverse [2+2] reaction involving cleavage of the cyclobutane ring occured at high temperatures with the formation of a series of farnesane epoxides **103**–**106**[80] (Scheme 28).



Scheme 20



Scheme 21

trans-Caryophyllene **1** will also undergo ene reactions involving the trisubstituted double bond. Adducts with maleic anhydride **107**[81] and formaldehyde **108**[82] have been isolated.

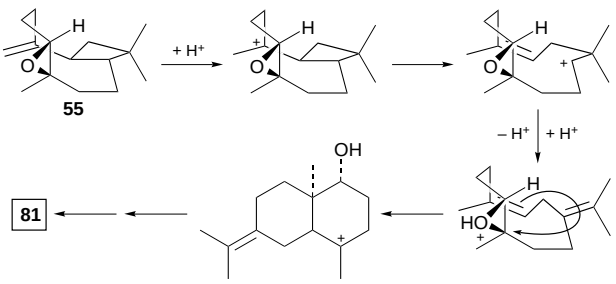
The unsaturated ketone **109**, a C-15 deoxy derivative of compounds found in *Pulicaria dysenterica*[83] and *Pulicaria arabica*,[84] has been synthesized from caryophyllene oxide **55** and undergoes an interesting dimerization (Scheme 29).

8 Radical rearrangements of *trans*-caryophyllene

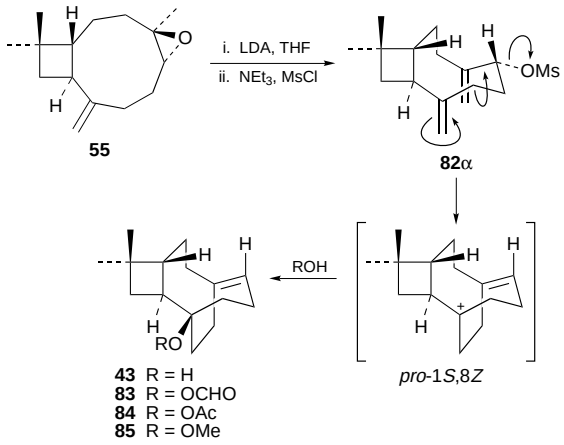
Caryophyllene nitrosite **110**, prepared initially in 1892[4,85] by treating *trans*-caryophyllene **1** with nitrous acid, absorbs radiation at 270 nm and also in the red region of the spectrum at 670 nm, giving rise to the blue colour of the solid. When the adduct was treated with iodine in chloroform, a stable nitroxide radical **111** was formed.[86] When the nitro nitroso adduct **110** was irradiated with red light in chloroform in the absence of air, it decomposed affording, *inter alia*, the dimer **112**[87] (Scheme 30). Various elimination reactions occur in the absence of solvent, leading to the formation of the unsaturated nitro compounds **112**, **113** and **114**.

When compound **110** is irradiated with ultraviolet light, the nitro group absorbs the radiation and generates the cyclization product **115** (Scheme 31).

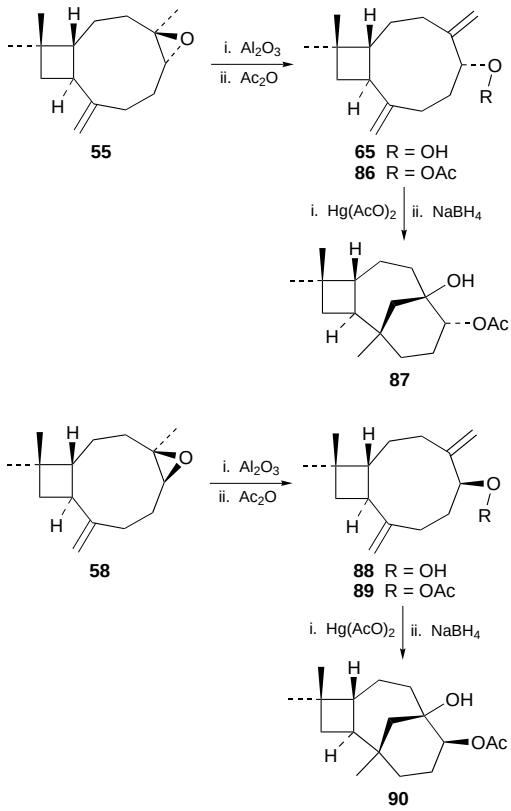
The radical addition of acetaldehyde to *trans*-caryophyllene **1**[89] takes place by attack on the endocyclic double bond. Cyclization of the tertiary radical at C-4 with C-8 generates compounds possessing the tricyclo[7.2.0.0^{4,8}]undecane skeleton (compounds **116**–**119**) (Scheme 32). The punctaporonines, sesquiterpene antibiotics produced by *Poronia punctata*,[90] possess this carbon skeleton.



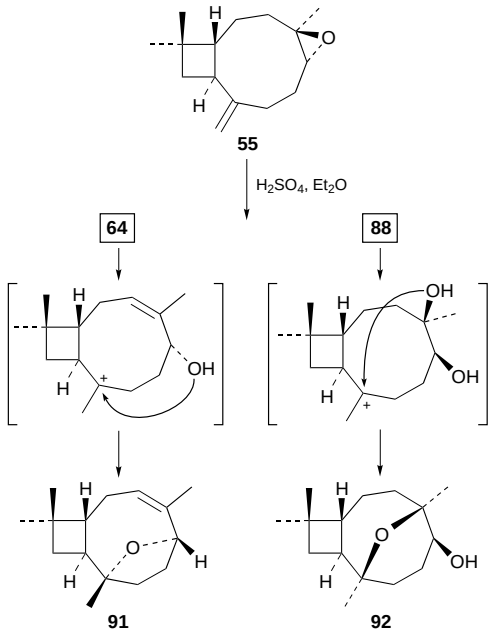
Scheme 22



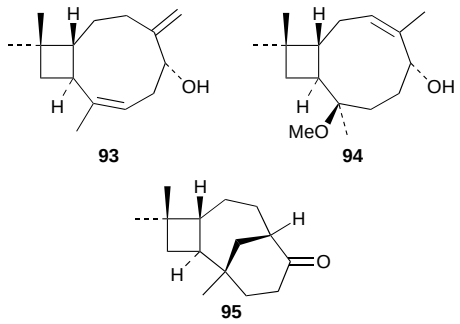
Scheme 23

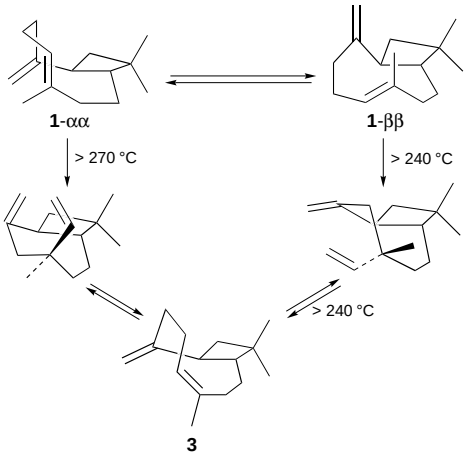


Scheme 24



Scheme 25



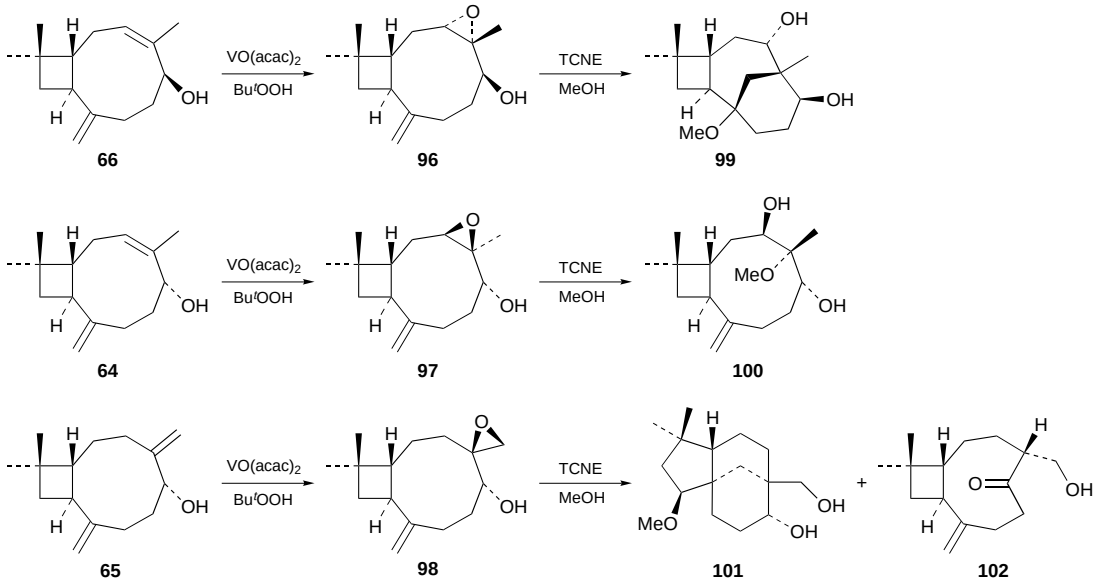


Scheme 27

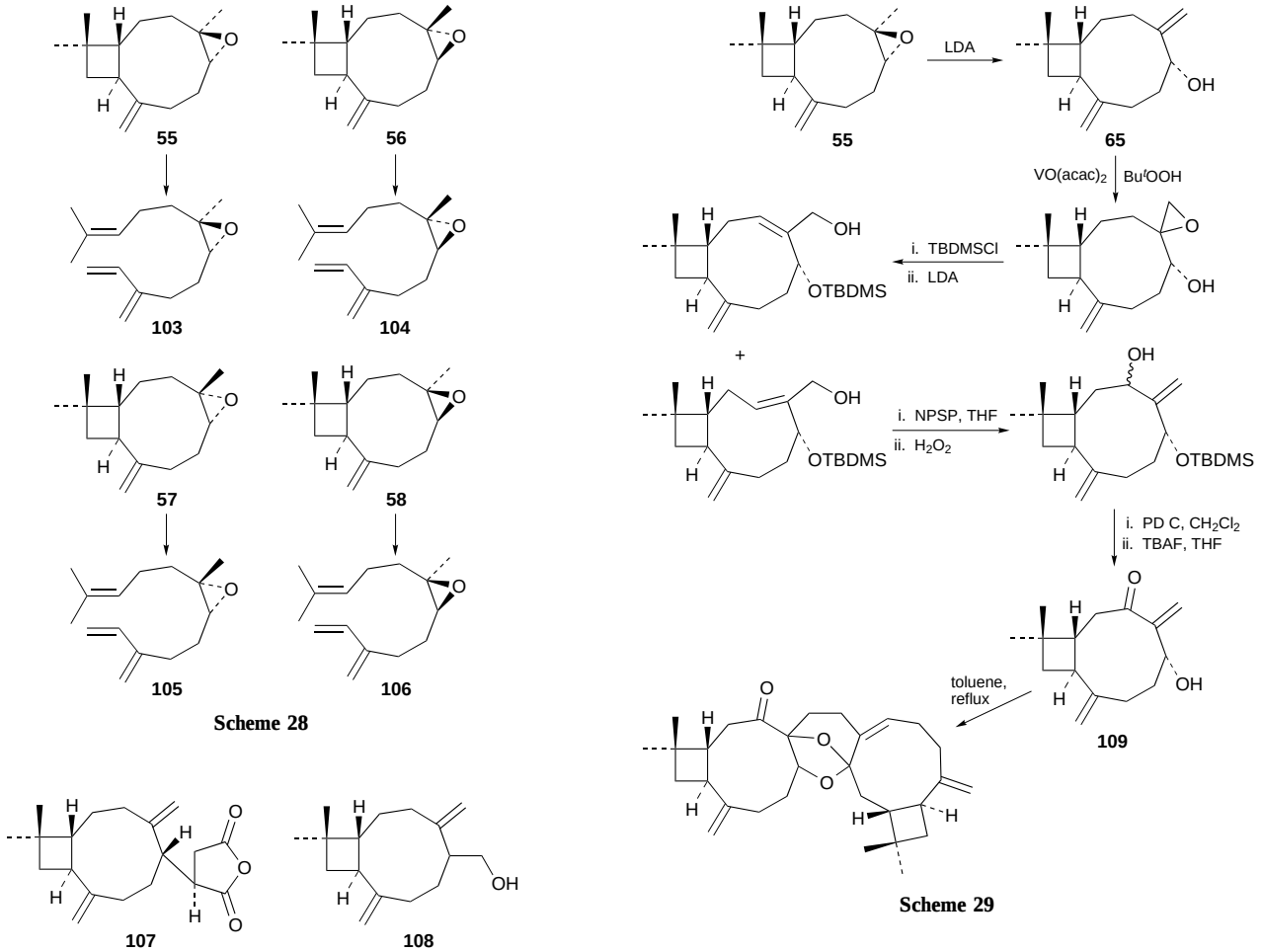
Compounds of this type have also been obtained from the epoxides of *trans*-caryophyllene **1** and isocaryophyllene **3** by reduction with lithium in liquid ammonia.[91] The stereochemistry of the products **120**–**127** (Scheme 33) clearly reflects the preferred conformation of the parent epoxides.

9 Reaction of the epoxides in alkali

Caryophyllene oxide **55** is exceptionally stable to base. It is not even attacked by caustic soda at 150 °C.[92] The conformation of the nine-membered ring prevents attack by an external



Scheme 26



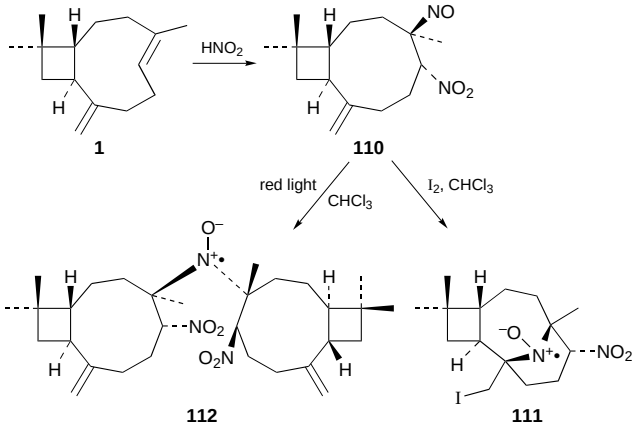
Scheme 28

Scheme 29

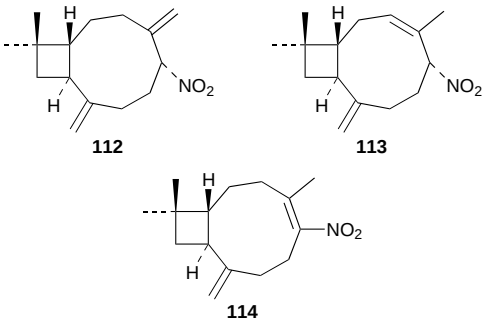
nucleophile on the rear-face of the epoxide. However, the nor-ketone kobusone **128** and its epimers **129** and **130** undergo intramolecular cyclization,[93] with the formation of compounds of the panasinsane skeleton (Scheme 34). Where the epoxide stereochemistry precludes this, as in **130**, a cyclopropane ring is formed. The structure of the product **132** from **128** has recently been revised to **138**.[94] The hydroxy ketones **133** and **134**, are formed by a transannular 1,4-hydride shift.

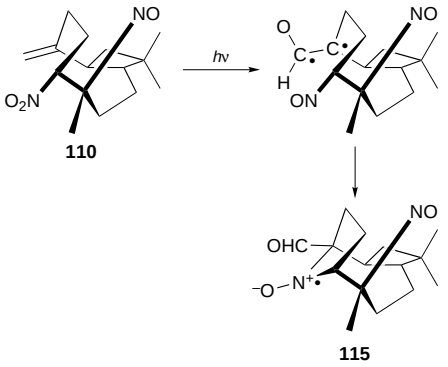
Further epoxidation and hydrolysis of the exocyclic double bond or glycol formation with osmium tetroxide, afforded a range of 8,13-diols which undergo intramolecular ether formation reactions[92] (Scheme 35, Scheme 36, Scheme 37 and Scheme 38).

When the bis-epoxides derived from **55** (compounds **140** and **141**) are treated with $LiAlH_4$ in THF,[95] four possible ethers might be formed, but only two were actually obtained (Scheme 39), compounds **142** and **143**. This result is in agreement



Scheme 30



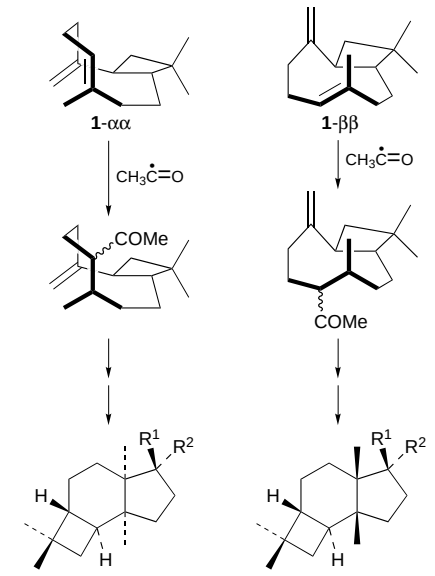


Scheme 31

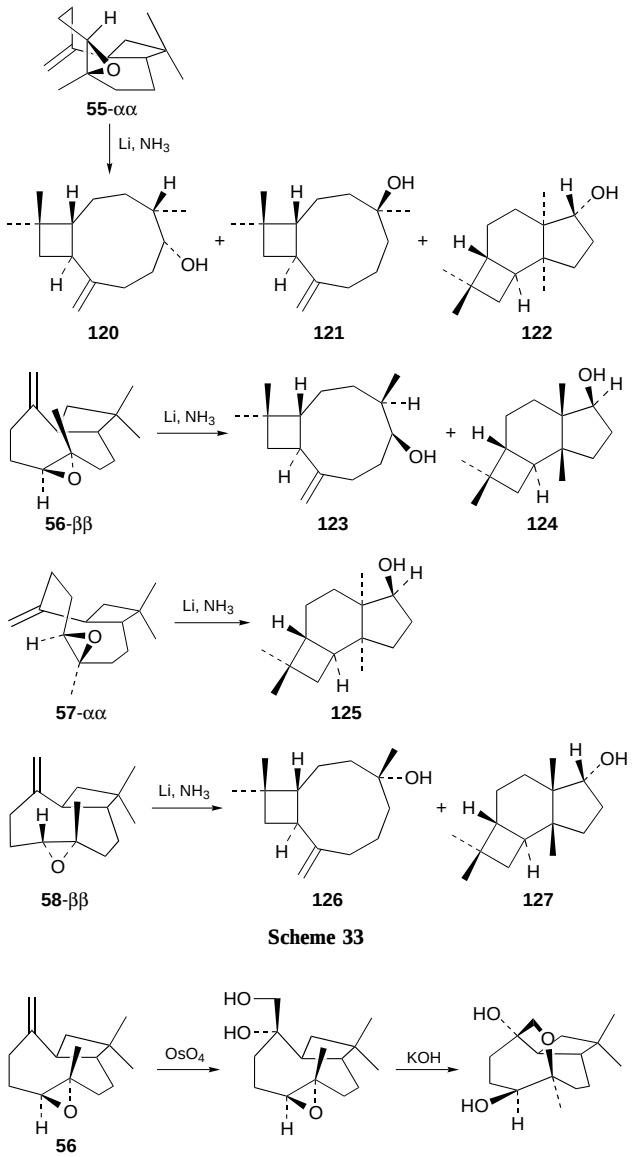
with the previously presented results (Scheme 35–38), because it is only from the bis-epoxides of **55** (**140** and **141**) that it would be possible to obtain ethers involving a tertiary alcohol precursor.

10 Oxidation and reduction of caryophyllene

trans-Caryophyllene **1** reacts in most cases initially on the endocyclic double bond substantially reducing the ring strain. Ozonolysis, for example, occurs firstly on the endocyclic double bond.[96] Monoepoxidation takes place selectively on the endocyclic double bond.[56] If the amount of peracid is raised, and the temperature and time are controlled, then bis-epoxidation products **141**, **140** or kobusone **128** are obtained.[95] Hence, in order to prepare the exocyclic epoxide **144**, *trans*-caryophyllene **1** was converted *via* its epoxide **55** and the nor-ketone kobusone **128**, to **9**, which was then converted to the epoxide **144** by a Corey–Chaikovsky reaction (Scheme 40).[97]

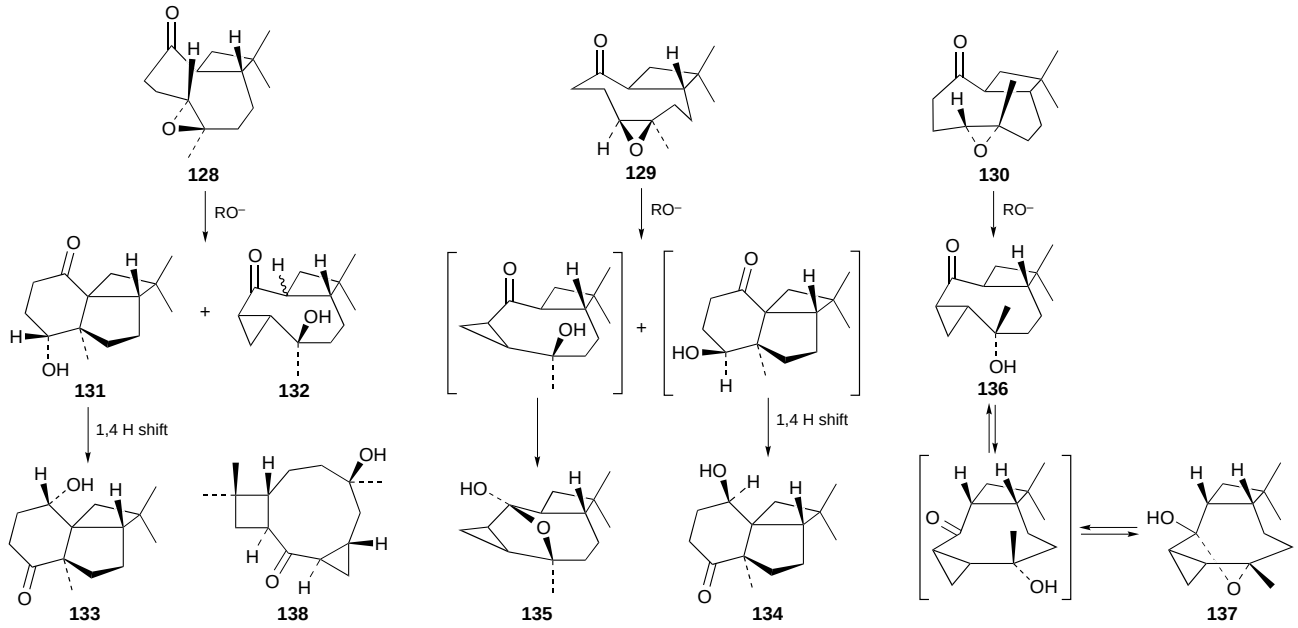


Scheme 32

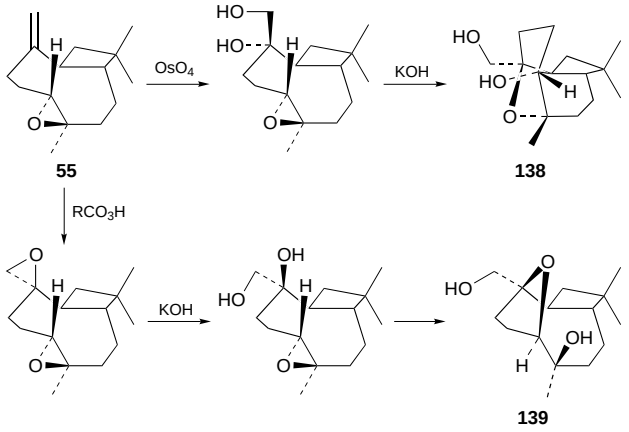


Scheme 33

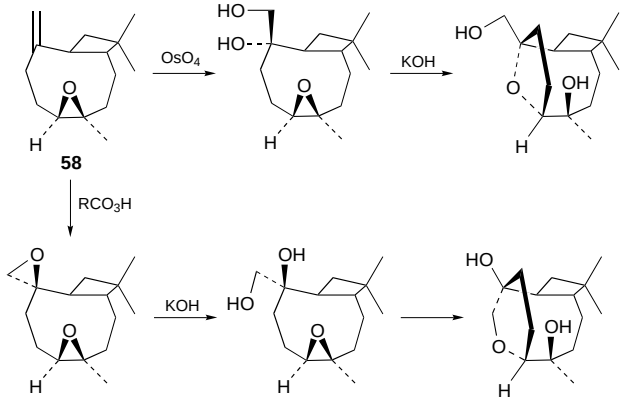
Scheme 35



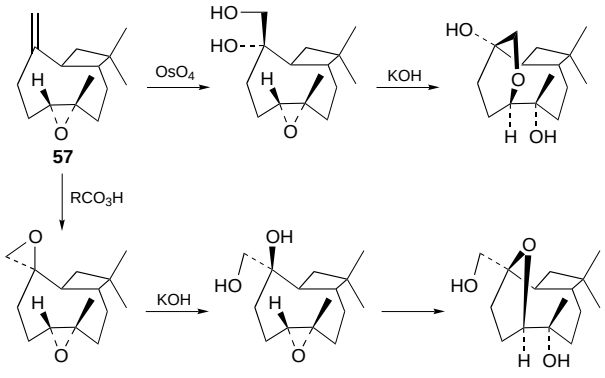
Scheme 34



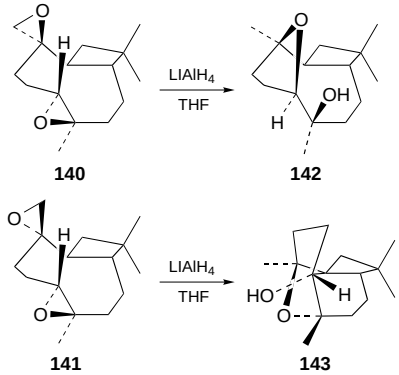
Scheme 36



Scheme 38



Scheme 37



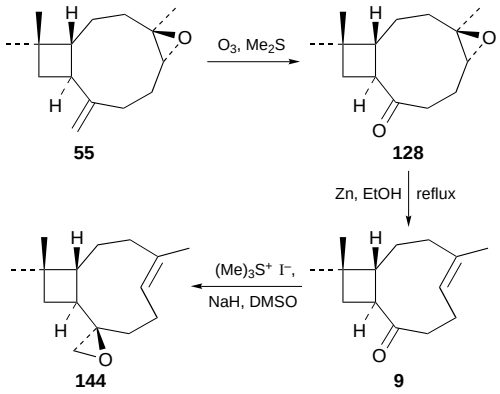
Scheme 39

trans-Caryophyllene **1** reacted with sulfur in the presence of light to form a 4,5-thiirane.

Autoxidation of *trans*-caryophyllene **1** and isocaryophyllene **3** in the presence of Bengal Red as a photosensitizer, led to a series of allylic alcohols **64**, **65**, **66**, **145**, **146** and **147**, again derived from reaction of the endocyclic double bond.[99]

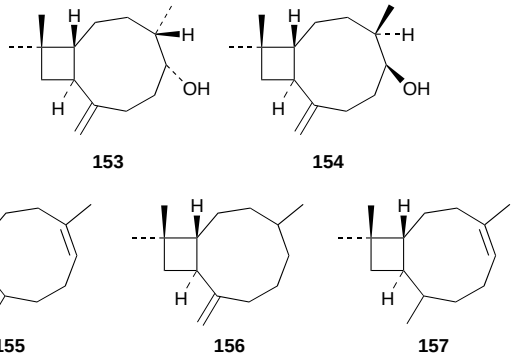
Oxidation of *trans*-caryophyllene **1** with lead tetraacetate[100] afforded a range of compounds (**55**, **56**, **64**, **65**, **66**, **43**, **147**, **148**, **149**, **150**, **151** and **152**) derived, with one exception **152**, from reaction of the endocyclic double bond. Compound **43**, with the triphyllane skeleton, may arise by cyclization of one of the allylic alcohols **65**.

Hydroboration of *trans*-caryophyllene **1**[101] took place exclusively on the endocyclic double bond to give the alcohols **153**

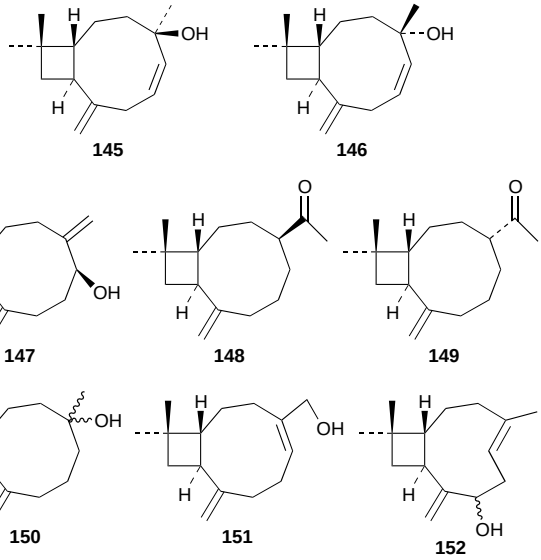


55 **128** **144** **9**

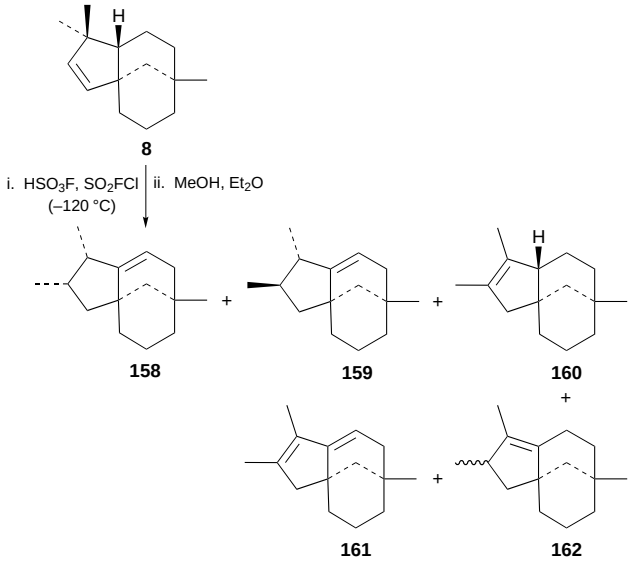
Scheme 40



153 **154** **155** **156** **157**

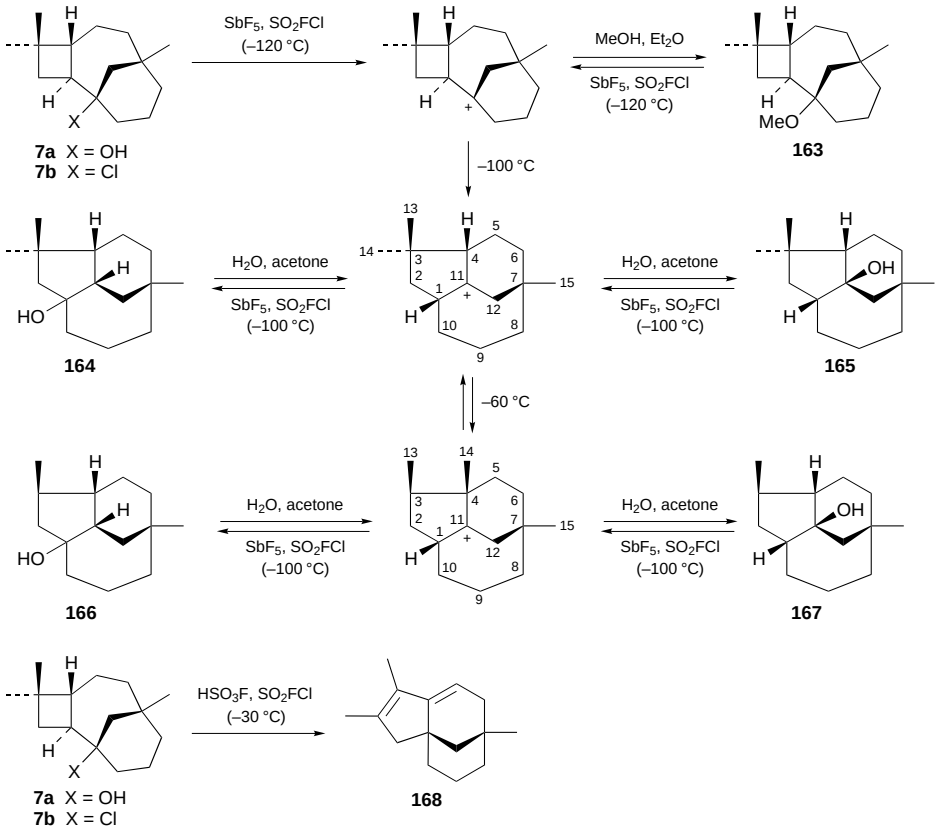


145 **146** **147** **148** **149** **150** **151** **152**



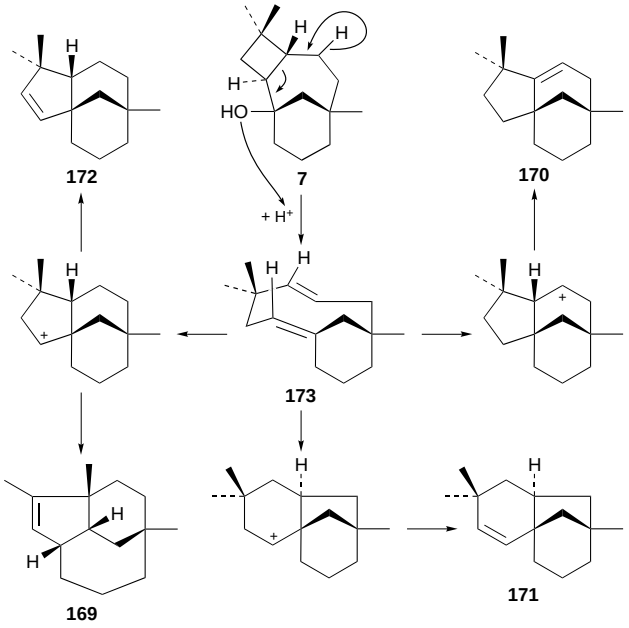
8 **158** **159** **160** **161** **162**

Scheme 41

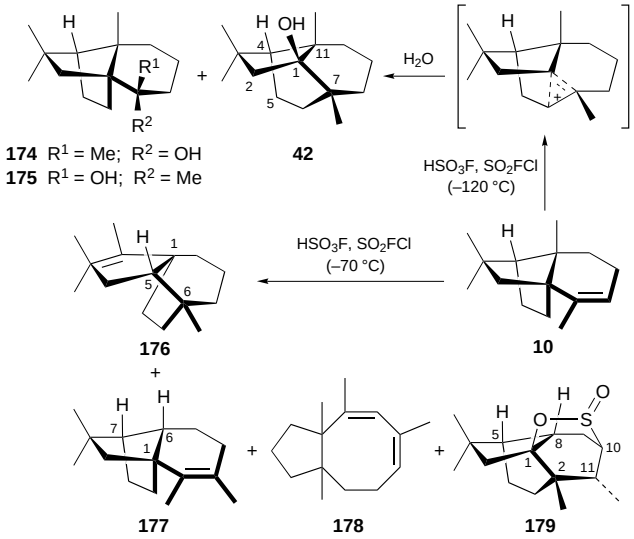


7a X = OH
7b X = Cl
163 **164** **165** **166** **167** **168**

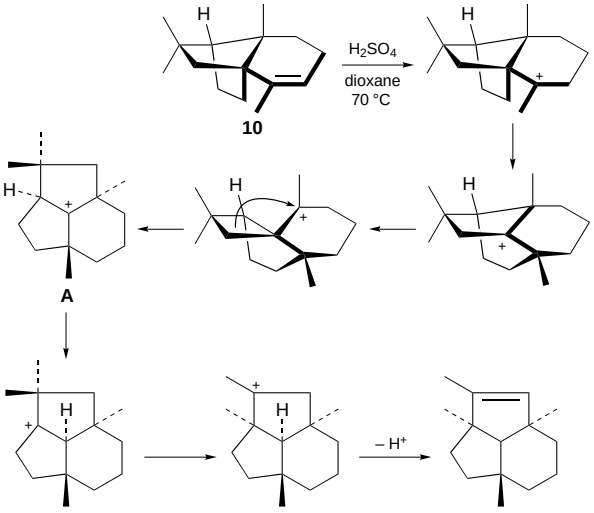
Scheme 42



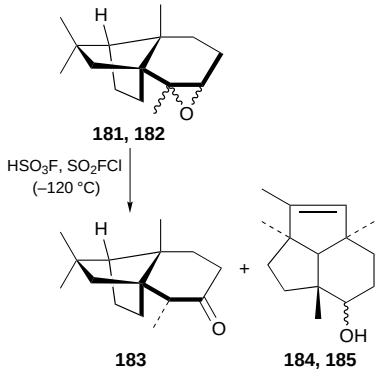
Scheme 43



Scheme 44



Scheme 45



Scheme 46

and **154** in amounts which reflected the proportions of the different conformers. However, isocaryophyllene **3**, with a less reactive endocyclic double bond, afforded the alcohol **155**. The endocyclic double bond of *trans*-caryophyllene **1** was reduced by diimide (compound **156**)[101] whilst it was the exocyclic double bond of isocaryophyllene **3** that reacted (compound **157**). However, catalytic hydrogenation, reflecting the ease of access of the double bond, reduced the exocyclic double bond of caryophyllene.

11 The rearrangements of clovene, neoclovene and caryolan-1-ol in acidic and super-acidic media

As noted previously the products obtained by treatment of *trans*-caryophyllene **1** with super-acid are the sum of the products from the reaction of clov-2-ene **8** and caryolan-1-ol **7**.

When clov-2-ene **8** was treated with the super-acid system HSO_3F–SO_2FCl at −120 °C and the reaction mixture then neutralized with methanol–diethyl ether, the olefins **158**, **159**, **160**, **161** and **162** were obtained.[25]

On the other hand, when caryolan-1-ol **7a** or its chloride were subjected to reaction with super acid, the products varied with the conditions.[102] At −120 °C in the presence of SbF_5–SO_2FCl followed by neutralization with methanol–diethyl ether, the methyl ether **163** was obtained (Scheme 42). At −100 °C rearrangements started to occur and the alcohols **164**, **165**, **166** and **167** were obtained after the reaction mixture was quenched with water in acetone. Finally at −30 °C the super-acid system HSO_3F–SO_2FCl gave the diene **168** after neutralization with the methanol–diethyl ether mixture. This compound was the enantiomer of **162**, obtained from clov-2-ene **8**. The formation of these products may be rationalized in terms of distinct sets of carbocations which cannot interconvert through their parent caryophyllene because of the barrier to conformational inversion under these conditions.

The rearrangements of caryolan-1-ol **7** in polyphosphoric acid[103] have been examined and the products which were isolated are shown in Scheme 43. The intervention of a diene **173** formed by fragmentation of the cyclobutane ring, may account for the products isoclovene **169**,[104] pseudoclovene A **170**,[105] pseudoclovene B **171**[106] and epiclovene **172**.[107]

Treatment of neoclovene **10** with super-acid[108] led to a series of products depending on the temperature. Reaction with HSO_3F–SO_2FCl at −120 °C and neutralization with water in acetone gave the alcohols **174**, **175** and **42**. The latter is ginsenol which has been isolated from the roots of *Panax ginseng*.[109] At −70 °C various skeletal rearrangements occur and the products are **176**–**179**.

In contrast to the reaction with super-acid, treatment of α-neoclovene **10** with sulfuric acid in dioxane at 70 °C gives exclusively the alkene **180** (Scheme 45). This compound does not appear amongst the products of super-acid treatment. However, the epoxides of neoclovene **10** (**181** and **182**), when treated with super-acid give the ketone **183** and the rearrangement products **184** and **185** (Scheme 46).[110] Compound **53**, obtained from the acid-catalysed cyclization of isocaryophyllene **3**, and derived from carbocation **A**, has been correlated with **180**,[55] supporting the proposed pathway (Scheme 45).

12 Conclusions

In conclusion, in this review we have shown that the unique chemistry of caryophyllene is dominated by the flexible conformations of the nine-membered ring and the consequent relative positions of the reactive functional groups. The various cyclizations may lead to other polycyclic naturally-occurring sesquiterpenoid skeleta, paving the way for partial syntheses and the exploration of the structure–biological activity relationships in these families of natural products.

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