Recent applications of the divinylcyclopropane–cycloheptadiene rearrangement in organic synthesis

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Abstract
This review summarizes the application of the divinylcyclopropane–cycloheptadiene rearrangement in synthetic organic chemistry. A brief overview of the new mechanistic insights concerning the title reaction is provided as well as a condensed account on the biological relevance of the topic. Heteroatom variants of this rearrangement are covered briefly.

Introduction
The first documented divinylcyclopropane–cycloheptadiene rearrangement dates back to 1960 occurring during studies of Vogel and coworkers [1,2] on the thermal rearrangement of small carbocycles. Although the desired cis-divinylcyclopropane (9) (see Scheme 1) could not be isolated using the depicted synthetic route (see 1 to 10), as 9 readily rearranged under the final Hofmann elimination conditions, the resulting cycloheptadiene 10 was described as well as the rearrangement of trans-divinylcyclopropane taking place at 200 °C. The elusive cis-divinylcyclopropane (9) was characterized ten years later by Brown and coworkers [3] using a low temperature and very short-timed Wittig reaction between cis-vinylcarbaldehyde 11 and methylenetriphenylphosphorane.

This review summarizes the recent synthetic applications of the divinylcyclopropane–cycloheptadiene rearrangement starting in 1991. Earlier classic syntheses of sesquiterpenes are described to underline the synthetic power in the total synthesis of sesquiterpenoid natural products. The title reaction has been subject to previous reviews [5,6], partial overlap with the
content of this review to other reviews concerning different topics exist [7-10]. The divinylcyclopropane–cycloheptadiene rearrangement will be abbreviated as DVCPR in the following. The divinylcyclopropane moiety and the resulting cycloheptadiene will be highlighted in red throughout. The Buchner ring expansion [11,12] as a special case of the DVCPR is not part of this review. The related vinylcyclopropane–cyclopentene rearrangement has been reviewed elsewhere [13,14].

Review
Mechanistic considerations
Transition state. Although the cis-divinylcyclopropane rearrangement is in fact a tethered version of the Cope rearrangement, it has to be noted that the preference of transition states (chair/boat) is opposite. Whereas the Cope rearrangement of hexa-1,5-diene 12 usually proceeds through chair-like transition state 12’ (see Scheme 2) and not through

Scheme 1: Vogel’s first approach towards the divinylcyclopropane rearrangement [4] and characterization of cis-divinylcyclopropane by Brown.

Scheme 2: Transition states for the Cope rearrangement and the related DVCPR. Ts = transition state.
the energetically disfavoured boat-transition state \(12''\) [15], the DVCPR only proceeds via boat-like transition state \(9nn'\) where both vinyl-moieties are in the endo-orientation regarding the cyclopropane [16]. The other transition states \((9xx'/9xn')\) would result in a cycloheptadiene with at least one \(E\)-configured double bond (13/14) after a hypothetical DVCPR, which can be regarded as inaccessible. Calculations revealed that the preferred orientation for \(cis\)-divinylcyclopropane is exo/exo \(9xx\). The first rotation of a vinyl-moiety into the endo-orientation requires 0.8 kcal/mol giving \(9xn\), the endo-orientation of both vinyl-moieties requires 2.9 kcal/mol represented as \(9nn'\) [17-19]. The necessary energy for the only possible transition state \(9nn'\) results in 19.7 kcal/mol, which is in good agreement with the experimental values of von Doering [20,21]. The rearranged cycloheptadiene 10 is favoured by \(-20.1\) kcal/mol compared to the corresponding \(cis\)-divinylcyclopropane (9).

Calculations have been carried out for \(cis\)-divinylheterocyclopropanes including nitrogen, oxygen, sulfur and phosphorus substitution [22], as well as \(cis\)-1,2-cyclobutanes [19,23]. Earlier calculations have been carried out for mono-heteroatom substitution in the vinyl moiety [24,25].

Transition state \(9nn'\) concludes that only \(cis\)-divinylcyclopropane undergoes the desired rearrangement, whereas \(trans\)-divinylcyclopropane should not react.

**Trans-cis isomerization.** Nevertheless, \(trans\)-divinylcyclopropane 15 (see Scheme 3) can be used in the DVCPR, as it undergoes isomerization to the desired \(cis\)-isomer 9 at elevated temperature (\(\approx 200^\circ C\) [1,2], lowered for more conjugated systems). The isomerization pathways have been suggested to proceed either via the formation of intermediate diradical-species (pathway A, Scheme 3) [16,20,26,27] or through one-center epimerization (pathway B) [28,29]. Following pathway A, the C1–C2 bond of 15 is cleaved homolytically to give diradical 16. The two radicals are stabilized as allylic radicals (depicted as \(16'\)), rotation around the C1–C3 bond takes place (16' to \(16''\)) followed by radical recombination to give \(cis\)-divinylcyclopropane (9). Pathway B proceeds through the formation of planar allylic anion 17, which undergoes inversion to give \(cis\)-divinylcyclopropane (9). An alternative reaction pathway of the \(trans\)-divinylcyclopropane (15) to yield the cycloheptadiene product is the direct formation of the seven membered ring from diradical 16.

**Biosynthetic applications**

The DVCPR has been shown to be part of the biosynthesis of ectocarpene (21, see Scheme 4) [29], an inactivated algae pheromone [30,31]. Starting from all-\(cis\)-pentaenic acid (18) peroxidation is supposed to take place to give 19, followed by formation of the active algae pheromone 20 upon enzyme

![Scheme 4: Proposed biosynthetic pathway to ectocarpene (21), an inactivated degradation product of a sexual pheromone of brown algae (20).](image)

### Scheme 3: Two possible mechanisms of trans-cis isomerizations of divinylcyclopropanes.
A divinylloxirane rearrangement has been proposed as the key step in the biosynthesis of several natural products containing a dihydrooxepine moiety. In the case of occidenol (25, see Scheme 5), which has been isolated from the wood of Thuja koraiensis, farnesyl pyrophosphate (22) is supposed to undergo ring closure and the intermediate carbocation is trapped by hydroxide to give hedycaryol (23) [33]. Oxidation leads to divinylloxirane 24, which rearranges to the corresponding dihydrooxepine, yielding occidenol (25) [34,35]. Miscandenin (26, isolated from Mikania species) [36] and dictyoxepin (27, isolated from brown algae) [37] are supposed to originate from the same cis-divinylloxirane rearrangement.

Gaich et al. [38,39] used the DVCPR in a biosynthetic investigation targeting the dimethylallyltryptophan synthase. In order to test the biosynthetic hypothesis of the mode of action of the 4-prenylation of indoles by Arigoni and Wenkert (starting from L-tryptophan and dimethylallyl pyrophosphate (DMAPP) through 28 to yield 29, (Scheme 6) [40-42] the spiro-oxindole 30 was synthesized. The system underwent a cis-aryl-vinyl-cyclopropane rearrangement [43] to give 31 followed by rearomatization in 4–12 hours at room temperature yielding tricycle 32. The formation of the obtained tricyclic cyclohepta[c]oxindole core 32 proved the synthetic versatility of a [3,3]-sigmatropic rearrangement for direct C–C-bond formation at the C4 position of the indole nucleus, and thus provides experimental evidence for the biosynthetic proposal.
Applications to natural product synthesis

Fatty acid metabolites

Iguchi and co-workers [44] applied the DVCPR to the total synthesis of the marine prostanoid clavubicyclone [45]. Known aldehyde 33 (see Scheme 7) [46] was subjected to Wittig conditions to furnish an intermediate lactone, which was then opened reductively followed by selective oxidation of the allylic alcohol to yield aldehyde 34. Addition of double deprotonated methyl acetoacetate gave β-ketoester 35. Diazotransfer followed by double protection resulted in the formation of compound 36. Rh-catalyzed intramolecular cyclopropanation of this compound gave bicyclic 37. Selective removal of the secondary protected alcohol through β-elimination yielded trans-divinylcyclopropane 38, which underwent DVCPR under forcing conditions after trans-cis-isomerization to obtain the desired bridged bicycle 39.

Reduction of ketone 39 (see Scheme 8) introduced a new stereocenter (10:1 selectivity), which was not assigned. The resulting major alcohol was protected, followed by saponifica-

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**Scheme 7:** Iguchi's total synthesis of clavubicyclone, part 1.

**Scheme 8:** Iguchi's total synthesis of clavubicyclone, part 2.
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Scheme 9: Wender’s syntheses of the two pseudoguainanes confertin (50) and damsinic acid (51) and Pier’s approaches towards four sesquiterpenoid natural products using the DVCPR with both trans- and cis-divinylcyclopropanes. The yields for 53 to 54 and 61 to 62 are stated as yield over several steps (77% over three steps and 98% over two steps, respectively).
propylene 53 underwent the desired DVCPR after trans-cis-isomerization of the vinyl moiety at 175 °C, forming bridged tetracyclic 54, which already contained the crucial seven-membered ring present in the target molecule 55. Intermediate 54 was advanced in ten steps to provide an intermediate aldehyde, which had been previously converted to the natural product in seven steps [55-57].

The total synthesis of the sesquiterpenoid sinularen (59) from the coral Sinularia mayi [58] started from alcohol 56, which was converted to bicyclic 57 in nine steps. Trans-divinylcyclopropane 57 was then subjected to high temperature DVCPR conditions furnishing bridged bicycle 58. Trans-cis isomerization of the vinyl moiety had to take place prior to the rearrangement to access the required boat transition state of the rearrangement. Intermediate 58 was converted to the natural product 59 in four additional steps.

Two other sesquiterpenoids, prezizaene (63) [59,60] and prezizanol (64) [60], isolated from Eremophila georgii or vetiver oil were synthesized starting from cyclopentene derivative 60 [61]. This rather simple starting material was elaborated to advanced bicyclic 61 in only seven steps. This time the group of Piers used a cis-divinylcyclopropane, which underwent smooth DVCPR during distillation at 110 °C to yield bridged bicycle 62. The desired natural products 63/64 were obtained after another ten or eleven steps respectively. For more “classic” applications of the DVCPR in total synthesis see reference [5].

Overman and coworkers [62-65] successfully applied the DVCPR as the key step in their total synthesis of the diterpene scopadulcic acid B (79) see Scheme 10, isolated from the Paraguayan plant Scoparia dulus [66]. Starting from 2-iodomobenzaldehyde (65) allyl-Grignard addition took place followed by TBS-protection of the resulting alcohol. The installed double bond was subjected to hydroboration/oxidation, followed by Swern oxidation of the resulting alcohol to yield aldehyde 66. Addition of cyclopoly-Grignard reagent 67 [67,68], followed by oxidation to the corresponding ketone yielded vinylcyclopropane 68. Deprotonation and TMS-protection furnished silyl-enoether 69, which underwent the desired DVCPR in almost quantitative yield at elevated temperature, followed by removal of the silyl-protecting group under acidic conditions to furnish cycloheptenone 70. Standard functional group interconversion furnished disiolefin 71. Subjection of this compound to Heck coupling conditions resulted in the formation of a bridged tetracycle after initial Heck coupling followed by carbo-palladation and subsequent β-hydride elimination [69-71]. Double bond regioisomers (between C7 & C8 or C13 & C14) were obtained. Oxidation with DDQ yielded the 1,6-unsaturated ketone 72. Selective epoxidation followed by reductive epoxide opening furnished the desired alcohol 73 [72]. Alcohol-directed 1,4-reduction using LiAlH4 [73] followed by ether formation gave methyl ether 74. Reduction of the remaining ketone moiety gave the equatorial alcohol exclusively. Ortholithiation followed by the addition of carbon dioxide [74,75] resulted in the formation of carboxylic acid 75. Birch reduction with concomitant methylation [76,77] followed by selective hydrogenation and reduction of the carboxylic acid resulted in the formation of alcohol 76. Installation of the remaining quaternary carbon center was achieved by the conjugate addition of cyanide [78]. Reduction of the newly introduced nitrile yielded the unexpected stable pentacycle 77. Formation of the missing methyl group (compound 78) could be achieved using forcing Wolff-Kishner-conditions. Benzoate formation and global oxidation [79,80] finally furnished scopadulcic acid B (79). A similar approach was used by the same group in their total synthesis of scopadulcic acid A [81].

Davies and coworkers [82] utilized the DVCPR embedded in a formal [4 + 3]-cycloaddition [83] in the total syntheses of the related sesquiterpene metabolites tremulenediol A (88, see Scheme 11) and tremulenediol A (89), isolated from a fungal pathogen [84]. Horner–Wadsworth–Emmons olefination of the starting ketone 80 [85] provided an E/Z-mixture of α,β-unsaturated ester 81. Deprotonation followed by an acidic quench resulted in deconjugation to give β,γ-unsaturated ester 82. Diazotransfer using p-ABSA [86] yielded diazoester 83. Selective rhodium-catalyzed cyclopropanation of the cis-double bond [87,88] of diene 84 [89] furnished cis-divinylcyclopropane 85, which underwent DVCPR upon Kugelrohr distillation at 140 °C to give bicyclic 86. Selective hydrogenation of the less substituted double bond using Wilkinson’s catalyst [90] gave α,β-unsaturated ester 87. Removal of the acetyl protecting group with concomitant lactonization concluded the total synthesis of tremulenediol A (88), whereas global reduction resulted in the formation of tremulenediol A (89).

Davies and co-worker [91,92] investigated the formal synthesis of the sequesterterpene-hydroquinone derivative frondosin B (99, see Scheme 12) [93] via an enantioselective cyclopropanation of trans-piperylene and subsequent divinylcyclopropane rearrangement, to further demonstrate the versatility of their formal [4 + 3] cycloaddition [82]. Starting from 4-methoxyphenol (90) Friedel–Crafts acylation and cyclization provided bicycle 91. Wittig olefination furnished benzofuran 92. Diazotransfer using p-ABSA yielded the crucial diazo compound 93, which was used in the following enantioselective cyclopropanation with the lesser substituted double bond of piperylene under Rh2(R-DOSP)4 catalysis. cis-divinylcyclopropane intermediate 94 underwent in situ DVCPR under the reaction conditions, and rearomatization of the benzofuran moiety provided 95. Reac-
Scheme 10: Overman's total synthesis of scopadulcic acid B.

The groups of Davies and Sarpong [97] teamed up for the total syntheses of the diterpenoids barekoxide (106, see Scheme 13) [98] and barekol (107) [99], isolated from the sponges *Chelonaplysilla erecta* and *Raspailia sp*. They envisioned a formal [4 + 3]-cycloaddition with an intermediate DVCPR [82]. Starting from diene 100, enantioselective cyclopropanation catalyzed by Rh2(R-PTAD)4 took place using vinyldiazo compound 101 to form cis-dinvinylcyclopropane intermediate 102.

tion of the less hindered double bond yielded tricycle 96, for which the yield and enantioselectivity was determined starting from 93. Standard functional group interconversion first provided exo-methylene 97, followed by ruthenium-catalyzed oxidative cleavage of the installed exo-methylene moiety [94] to give tricyclic ketone 98, which can be converted to frondosin B (99) in three steps according to Danishefsky and co-workers [95,96].
Scheme 11: Davies' total syntheses of tremulenolide A and tremulenediol A.

Scheme 12: Davies formal [4 + 3] cycloaddition approach towards the formal synthesis of frondosin B.
Scheme 13: Davies and Sarpong formal [4 + 3]-cycloaddition approach towards barekoxide (106) and barekol (107), involving a DVCPR.

Rearrangement yielded tricycle 103 in both good yield and good diastereomeric ratio. Selective hydrogenation of the more electron rich double bond followed by reduction of the ester furnished α,β-unsaturated ketone 104 after PPTS-catalyzed elimination of water. Subsequent Dibal-H reduction yielded the alcohol epimer 105 of barekol (107). Deoxygenation with concomitant isomerization of the double bond according to Gevorgyan [100] was followed by epoxidation to provide barekoxide (106). Acid-catalyzed isomerization finally yielded barekol (107).

Davies and coworkers [101-103] used the formal [4 + 3]-cycloaddition approach to access the diterpene 5-epi-vibsanin E (115), from the plant *Viburnum awabuki* (see Scheme 14) [104]. Starting from triene 108 cyclopropanation was achieved using vinyldiazo compound 101. The formal [4 + 3]-cycloaddition proceeded through cis-divinylcyclopropane 109 to yield rearranged cycloheptadiene 110. Desilylation was achieved using TBAF, followed by formation of a vinyl triflate and Stille coupling with tributyltin hydride. The oxidation state of the remaining ester was adjusted to the corresponding aldehyde, followed by a Lewis acid-catalyzed intramolecular inverse-electron-demand hetero-Diels–Alder reaction to give tricycle 111. The enol ether moiety was reduced using NaCNBH₃, followed by allylic Riley oxidation and PCC-mediated enone formation. Copper-catalyzed conjugate addition in the presence of TMSCI [105] yielded silyl enol ether 112. Subsequent introduction of the side chain in 113 via a Claisen rearrangement was followed by MOM-cleavage. Oxidation furnished an intermediate aldehyde, followed by Wacker oxidation and the Anders–Gaßner variant [106-109] of the Wittig reaction to furnish 5-epi-vibsanin E (115).

Echavarren and coworkers [110] used a DVCPR to target the sesquiterpenoid schisanwilsonene A (126, see Scheme 15), isolated from *Schisandra wilsoniana* [111], a plant used in traditional Chinese medicine. Submission of 1,6-enyne 116 to cationic gold-catalyst 117 led to 5-exo-dig cyclization and intermediate formation of bridged bicycle 119. Subsequent 1,5-acyl-shift afforded vinylcarbenoid 120, which underwent cyclopropanation with the added olefin 118 to give bicycle 121 in decent yield. Double deprotection followed by selective acetal-protection of the less hindered alcohol and oxidation of the remaining unprotected alcohol moiety led to aldehyde 122. Wittig olefination resulted in the formation of non-isolated cis-divinylcyclopropane 123, which immediately underwent DVCPR to give...
Scheme 14: Davies formal [4 + 3]-cycloaddition approach to 5-epi-vibsanin E (115) containing an intermediate cis-divinylcyclopropane and the corresponding DVCPR.

Alkaloid targets

Davies and co-worker [112] were the first to apply the DVCPR to the total synthesis of alkaloids. Anhydroecgonine methyl ester (131, see Scheme 16) is a tropane alkaloid structurally related to cocaine, which can be detected in the human body after cocaine consumption. It can be degradatively accessed from cocaine through pyrolysis, cocaine congeners can be prepared via conjugate addition afterwards [113,114]. Boc-protected pyrrole 127 was subjected to rhodium-catalyzed cyclopropanation with vinyldiazo compound 128 [115,116], bearing a chiral auxiliary [117]. The intermediate cis-divinylcyclopropane 129 rearranged to the corresponding bridged cycloheptadiene 130 in a DVCPR. The chiral auxiliary was removed in the following using methanolysis conditions, followed by reduction of the more electron rich double bond and reductive amination after Boc-deprotection to yield the desired natural product 131 in only five steps.

Perhaps one of the most prominent alkaloid syntheses using a DVCPR was carried out by Fukuyama and coworker [118-120] and targeted gelsemine (146, see Scheme 17 and Scheme 18), an alkaloid with a unique hexacyclic cage structure isolated from Gelsemium Sempervirens [121,122]. Starting from methyl acetoacetate (132), double deprotonation and addition of the more reactive anion to sorbal aldehyde furnished the corresponding alcohol, which was immediately protected as its acetal 133 using ethyl vinyl ether. The necessary diazo moiety was installed using tosylazide as a diazo-transfer reagent to yield 134. Copper catalyzed intramolecular cyclopropanation furnished bicycle 135. Reduction of the carbonyl moiety and protection of the resulting alcohol was followed by ether cleavage and ozonolysis to give aldehyde 136 [123]. Knoevenagel condensation with 4-iodooxindole was achieved in the next step. Pfitzner–Moffatt oxidation [124] followed by elimination furnished trans-divinylcyclopropane 137. Submission of this compound to elevated temperature initiated a very smooth DVCPR yielding bicycle 138. The temperature for the preceeding trans-cis divinylcyclopropane isomerization was unusually low. This can be rationalized by the substitution of the divinylcyclopropane with two electron withdrawing groups and the resulting stabilization of the intermediate(s).
Scheme 15: Echavarren’s total synthesis of schisanwilsonene A (126) featuring an impressive gold-catalyzed cascade reaction and a DVCPR.

Scheme 16: Davies early example of a formal [4 + 3]-cycloaddition in alkaloids synthesis.

The surplus iodine at the oxindole was crucial for the stereochemical control of the spiro-indolinone system in 138, it was removed in the next step using radical conditions. Horner–Wadsworth–Emmons olefination on the carbonyl moiety followed by protection of the oxindole gave intermediate 139. Conjugate addition of methylamine and protection of the amine was followed by selective reduction of the methyl ester [125]. Protection of the resulting alcohol gave tetracycle 140.

The remaining ester 140 (see Scheme 18) was then converted to the corresponding acid, followed by anhydride formation. Introduction of an acyl azide resulted in a Curtius rearrangement, upon heating the intermediate isocyanate was trapped with EtOH to yield ethyl carbamate protected amine 141. Deprotection of the Alloc-group [126] and chloro carbamate formation furnished 142. Exposure of this compound to a silver source led to the formation of the five-membered lactam, together with an acylimine. This was removed under acidic conditions to furnish aldehyde 143. Tebbe olefination [127] installed the missing double bond in 144. Oxymercuration [128] followed by reductive biphasic demercurization [129] furnished the remaining tetrahydropyran ring, yielding 145. Removal of the MOM-protecting group followed by reduction of the amide concluded Fukuyama’s total synthesis of gelsemine (146).

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Scheme 17: Fukuyama’s total synthesis of gelsemine, part 1.

Scheme 18: Fukuyama’s total synthesis of gelsemine, featuring a divinylcyclopropane rearrangement, part 2.
An approach similar to Davies formal [4 + 3]-cycloaddition [81] was used by the group of Kende [130] to access the alkaloid isostemofoline (158, see Scheme 19) [131]. Rhodium-catalyzed cyclopropanation of silyl-enol-diazo compound 101 and Boc-protected pyrrole 147 resulted in the formation of intermediate cis-divinylcyclopropane 148, that rearranged under the reaction conditions to give the corresponding highly substituted bridged cycloheptadiene 149. Deprotection of the enolate, reduction of the remaining double bond and subsequent Krapcho decarboxylation [132] resulted in less functionalized ketone 150. Aldol condensation with furfural followed by O-allylation and Claisen rearrangement furnished enone 151. Standard functional group interconversiones were used to access TIPS-protected alcohol 152. Addition of methylithium at low temperature [133] resulted in stereoselective conjugate attachment of the required methyl group. Deprotection of the alcohol and transformation into a suitable leaving group yielded tosylate 153. Next, the furan was cleaved oxidatively, the resulting acid was converted to the corresponding anhydride, which could be reduced to the alcohol using NaBH₄, followed by reoxidation with DMP to yield aldehyde 154. Attachment of furanone enolate 155 [134,135], followed by reoxidation yielded tricycle 156. Deprotection of the amine and the MOM-protected alcohol led to a rearrangement cascade, which smoothly yielded hexacycle 157. This compound could be converted into isostemofoline (158), albeit in low yield. Isostemofoline could not be interconverted into stemofoline (159) using trifluoroacetic acid [136].

Danishefsky and coworkers [137-139] applied the DVCPR in their total synthesis of gelsemine (146, see Scheme 20 and Scheme 21). Starting from bicycle 160 [140] epoxidation using mCPBA furnished epoxide 161 [141,142], which could be converted into vinylcyclopropanecarbaldehyde 162 upon

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**Scheme 19:** Kende’s total synthesis of isostemofoline, using a formal [4 + 3]-cycloaddition, including an intermediate DVCPR.
rearrangement. Olefination using HWE-reagent 163 yielded intermediate cis-divinylcyclopropane 164, which underwent the desired rearrangement at remarkably low temperature to yield bicycle 165. Selective hydroboration/oxidation (directed through participation of the untouched double bond) followed by Swern oxidation gave ketone 166. The enone system 167 was prepared through addition of Eschenmoser’s salt, followed by Hoffman elimination of the resulting amine. Luche reduction [143] from the less hindered side followed by hydroboration/oxidation gave diol 168. Mono-mesylation of the primary alcohol followed by the addition of base furnished the signature oxetane moiety. Ether cleavage [144] and Swern oxidation resulted in the formation of ketone 169. HWE-olefination followed by reduction to the allyl alcohol led to allylic ester 170 after a Johnson–Claisen rearrangement [145] upon treatment with triethyl orthoacetate.

Ester 170 was saponificated (see Scheme 21), followed by the formation of an acid-azide. Shiori version [146,147] of the Curtius rearrangement with concomitant addition of MeOH to the intermediate isocyanate afforded carbamate 171. Oxtane 171 was then opened under Lewis-acidic conditions. The deprotected alcohol was protected to give pentacycle 172. Reduction of the nitro group was followed by Cbz-protection. Allylic alcohol 173 resulted from radical allylic bromination followed by displacement of bromine through water under silver-catalysis. Eschenmoser–Claisen rearrangement [148] led to the formation of the remaining quarternary carbon center, the resulting amide cyclized during the purification on silica to give amide 174. Reduction of this amide to the aminal was followed by dehydration and Lemieux–Johnson [149] oxidative cleavage to give dialdehyde 175. The liberated alcohol moiety was protected, followed by cleavage of the amide under basic conditions. Cyclization and Ley–Griffith oxidation [150] took place, followed by deprotection of the alcohol to give spiro-oxindole 176. The formation of the remaining tetrahydropyran was much in line with Fukuyama’s synthesis, utilizing the same oxymercuration/reductive demercuration [128,129] sequence (through intermediate 177) yielding 178. The oxindole protecting group was then removed, followed by reduction of the carbamate to the remaining missing methyl group [151] to finish gelsemine (146).

The total synthesis of the monoterprenoid-indole alkaloid gelsemoxonine (197, see Scheme 22) [152], isolated from the leaves of *Gelsemium elegans* was accomplished by Fukuyama and coworkers [153,154]. Starting from furfuryl alcohol (179) an epoxide initiated Achmatowicz reaction [155] took place to give α,β-unsaturated pyrone 180. Next in line was an enzyme catalyzed dynamic kinetic resolution [156], albeit with unsatis-
factory enantiomeric excess. The undesired enantiomer was then selectively cleaved using another enzyme with reversed selectivity to give enantiopure pyranone 181. Cyclopropanation was achieved using a Michael addition initiated ring closure yielding diester 183. Complete reduction furnished triol 184, followed by mono-protection of the least hindered alcohol. The remaining alcohol moieties were then oxidized to the corresponding keto-aldehyde 185. A two-step procedure was employed to generate $\alpha,\beta$-unsaturated oxindole-$N$-methoxide 187 [157,158]. Formation of silyl enol ether 188 furnished the desired cis-divinylcyclopropane, which underwent smooth DVCPR under mild conditions to give bridged bicycle 189. The alcohol was deprotected and oxidized to aldehyde 190. The aldehyde was transferred into the corresponding cyanohydrin trimethylsilyl ether using TMSCN [159-161], followed by protonation of the TMS-enolate and esterification of the intermediate acyl cyanide yielding allyl ester 191. This ester was transferred into the corresponding carboxylic acid, followed by formation of the acid chloride. The chloride was displaced with an azide, which underwent Curtius rearrangement upon heating. The intermediate isocyanate was intercepted by benzyl alcohol to provide secondary Cbz-protected amine 192. Bredereck’s reagent (193) [162] was used to generate enamine 194. The enol-form of the remaining carbonyl moiety was transformed into the corresponding vinyl chloride using Vielsmeier’s reagent [163,164]. Dechlorination [165,166] was then achieved and yielded $\alpha,\beta$-unsaturated aldehyde 195 upon hydrolysis. Grignard addition to the newly formed aldehyde followed by reoxidation furnished the side chain of compound 196. Treatment of unsaturated ketone 196 with Triton B and TBHP
yielded the epoxide resulting from top-face attack. The surplus Cbz-group was then deprotected using TMSI [167,168]. The final azetidine formation took place upon refluxing in ethanol to give gelsemoxonine (197).

**Further synthetic applications**

The group of Wender applied the DVCPR in an approach towards the core skeleton of tiglianes (like phorbol 206, see Scheme 23), daphnanes and ingenanes [169] in 1980 [170]. Starting from α-bromoenone 198 a Corey–Chaykovsky cyclopropanation reaction was achieved to yield cyclopropane 199. The keto-group was removed using a three step sequence, with concomitant reduction of the ester to give alcohol 200. Oxidation and Wittig olefination gave olefin 201. Lithium bromide exchange followed by 1,2-addition to ketone 202 yielded tricyclic 203, which was immediately subjected to acidic hydrolysis to give the desired tricyclic core skeleton 205 in 51% yield through transition state 204.

The group of Davies [171] demonstrated the impressive synthetic power of the DVCPR in their core structure synthesis of CP-263,114 (212, see Scheme 24) [172,173]. Subjection of
Scheme 23: Wender’s synthetic access to the core skeleton of tiglianes, daphnanes and ingenanes.

Diazofuran 207 to rhodium catalysis resulted in the formation of 209, 210 and 211 in solvent-dependent ratios. The sole product arising from the desired DVCPR via 208'' is the major product 210. The two remaining products arise from trans-silylation and fragmentation (208' to 209) or via ionic intermediate 208''' and fragmentation to give 211. The different product distribution can be controlled by the choice of the solvent. Notably cycloheptadiene 210 arising from the DVCPR contains two as well as the related trans-silylated compound 209. This demonstrates the huge driving force of the DVCPR, as two highly strained olefins are favoured over a cyclopropane-moiety.

Wood and coworkers [174] applied the DVCPR in the core structure synthesis of actinophyllic acid (218, see Scheme 25) [175]. Subjection of diazo compound 213 to copper catalysis yielded vinylcyclopropane 214. Deprotonation and silyl ether

Scheme 24: Davies’ approach towards the core skeleton of CP-263,114 (212).
formation resulted in intermediate cis-divinylcyclopropane 215, which smoothly underwent DVCPR to give cyclohexane 216. Tsuji–Trost allylation [176,177] furnished the quartenary carbon center. A two-step Fischer-indole strategy [178,179] finished tetracycle 217 under forcing conditions.

Takeda and coworkers [180] set out to investigate the use of an anionic oxy-cis-divinylcyclopropane rearrangement to build up the diterpenoid cyanthin skeleton [181-183] like that of allocyathin B2 (226, see Scheme 26), which was isolated from bird’s nest fungi [184-189]. Starting from α,β-unsaturated ketone 219 addition of ethynylmagnesium bromide took place, followed by a Rupe rearrangement [190] using refluxing acetic acid as solvent to give ketone 220. Addition of deprotonated ketone 220 onto acryloylsilane 221 [191] gave alkoxy intermediate 222, which underwent a Brook rearrangement followed by cyclopropane formation to yield anionic 223 in situ [192]. The aforementioned anionic oxy-cis-divinylcyclopropane rearrangement took place, yielding tricycle 224. DIBAL–H reduction gave the corresponding alcohol stereoselectively, followed by removal of the TMS-group at C10 with NBS and further enone formation upon treatment with TBAF to give tricyclic core skeleton 225 [192]. This reaction sequence constitutes a very nice example of a formal [4 + 3]-cycloaddition, without the use of a transition metal catalyst.

Donaldson and coworkers [193] used the DVCPR en route towards the core skeleton of the sesquiterpenoid guianolide family [194,195]. Starting from readily prepared vinyl bromide 227 (see Scheme 27) formation of the corresponding Grignard species was accomplished, followed by addition to organoiron complex 228 to give (pentenediyl)iron complex 229. Oxidation led to the formation of the desired divinylcyclopropane, followed by reduction of the ester to the desired alcohol to give
compound 230. Subjection of the trans-cis-divinylcyclopropane mixture to elevated temperature smoothly formed the desired bicycle 231. The less hindered double bond was removed using Wilkinson’s catalyst, followed by standard functional group interconversions to yield epoxide 232. When this compound was subjected to oxidative conditions both alcohols were oxidized to the corresponding aldehyde/ketone. Base-induced epoxide opening led to the formation of a double bond (C4/C5) and concomitant lactol-formation. The lactol was oxidized to the corresponding lactone under the same reaction condition. Final reduction gave core skeleton 233.

DVCPR in tandem reactions

The group of Stoltz [196,197] succeeded in establishing a tandem Wolff rearrangement/divinylcyclopropane rearrangement strategy [198]. Readily accessible α-diazo ketone 234 (see Scheme 28) was shown to undergo Wolff rearrangement [199] upon treatment with silver benzoate. The intermediate ketene 235 underwent stereospecific DVCPR through transition state 235’ under the reaction conditions to give enone 236 in excellent yield. This constituted the first example of the direct formation of an enone through a DVCPR.

Stephenson and coworker [200] found an intriguing example of a light mediated radical cyclization/arylvinylcyclopropane rearrangement. Subjecting cyclopropyl bromide 237 to an Ir-polypyridyl catalyst and visible light initiated the desired photoredox cascade forming a cyclopropylradical, which readily cyclized in an 5-exo-dig fashion. Radical quenching gave cis-arylvinylicyclopropane 238. Arylvinylicyclopropane rearrangement was followed by rearomatization to give tetracycle 239 (see Scheme 29).

Padwa and coworkers [201] discovered an intermediate DVCPR during their investigation of rhodium-catalyzed cyclizations of alkylnyl substituted α-diazo ketones. Transition metal-catalyzed diazo-decomposition of compound 240 (see Scheme 30) resulted in the formation of metallacyclobutene 241, followed by rapid metallacycloreversion to give carbenoid species 242. Intramolecular cyclopropanation furnished divinylcyclopropane 243, which underwent DVCPR under these conditions to give tetracycle 244 in 50% yield.

Matsubara and coworkers [202] investigated the formation of cyclohepta-1,3-diones from 1,2-diketone starting materials. Treatment of 245 with bis(iodozincio)methane resulted in the formation of cis-divinylcyclopropane 246 as the corresponding bis-zinc-enolate species. DVCPR occurred at ambient temperature, final acidic workup provided cycloheptadione 247 in excellent yield (see Scheme 31).
Toste and coworkers [203] reported a tandem gold-catalyzed Claisen rearrangement from popargyl vinyl ether 248 (see Scheme 32) to give intermediate vinyl-allencyclopropane 249, followed by a DVCPR to furnish cycloheptadiene 250.

1,2-Shift and vinyl-carbenoid formation sequences

Two major pathways to generate divinylcyclopropanes using transition metal catalysis have been developed. Uemura and coworkers [204] were the first to apply the transition metal catalyzed 1,2-acyl shift with subsequent vinyl carbenoid formation. Propargylic acetate 251 (see Scheme 33) has been shown to undergo 5-exo-dig cyclization via 252 to give zwitterionic intermediate 253. A concomitant fragmentation reaction yielded vinyl-carbenoid 254. Uemura and coworkers used this chemistry with propargylic acetate 255 to achieve cyclopropanation with various dienes, for example cyclopentadiene 256. Heating of this mixture of compounds resulted in the formation of bridged tricycle 257 in good yield. Toste and coworkers [205] discovered a 1,2-pivaloyl shift and cyclopropanation of the resulting...
gold-carbenoid from \(258\) with enyne \(259\) to yield vinylalkynecyclopropane \(260\). This compound was shown to undergo a gold catalyzed DVCPR to yield \(261\). Note that this reaction does most likely proceed via a step wise mechanism and involves charged intermediates.

Nevado and coworkers [206] applied a closely related reaction to propargylic acetate \(262\) using a cationic gold(I) catalyst, which was used to selectively cyclopropanate the less hindered double bond of dienes like \(263\). Spontaneous DVCPR provided cycloheptadiene \(265\) via \(264\) in good yields.

Further contributions to the topic have been put forward by the group of Echavarren [207] and Gung [208].

### Cycloisomerization involving DVCPR

Iwasawa and coworkers [209] discovered a cyclopropanation/DVCPR sequence of alkyne-substituted silyl enol ethers (for example \(274\), see Scheme 34) catalyzed by in situ formed \(\text{W(CO)}_3(\text{tol})\) upon irradiation to give annulated tricycle \(275\). The common mechanism for this type of reaction proceeds via endo-dig cyclization of enynes like \(266\) to give zwitterionic intermediate \(267\). Metal-carbenoid formation with subsequent cyclopropane formation gives rise to either cis- or trans-divinylcyclopropanes \(268/271\). cis-Divinylcyclopropane \(271\) can readily undergo DVCPR to give bicycle \(272\). 1,2-Migration of the migrating group \(G\) leads to final bicycle \(273\) after regeneration of the catalyst. Trans-divinylcyclopropane \(268\) can undergo DVCPR after 1,2-migration and subsequent formation of cis-divinylcyclopropane \(269\) yielding bridged bicycle \(270\).

Chung and coworkers [210] discovered a related reaction pattern using platinum(II) as the catalyst. Depending on the at-
tached rests on enyne 276 both possible cycloheptadienes (bridged 277 or annulated 278) could be accessed. The selective formation of annulated bicycle 278 in preference of the possible bridged variant underlined the preferred reactivity of their enyne system.

Gagosz and coworkers [211] recently showed that the cycloisomerization of enynes can be catalyzed by gold(I) catalysts. In a particular striking example propargylic alcohol 279 could be converted into bicyclic ketone 281 in good yields.

### Heteroatom variants

The oxygen substituted versions of the DVCPR have been subject to more intense research in the covered time period than the corresponding nitrogen variants. In general there are two different modes for the heteroatom incorporation into the DVCPR, as part of the cyclopropane moiety or as part of one of the vinyl moieties. All variants are covered in the following.

The Reisman group [12,212] observed an intermediate vinylcyclopropane carbaldehyde rearrangement on their way towards the total synthesis of salvileucalin B (292, see Scheme 35) isolated from the plant *Salvia leucantha* [213]. Starting from enantiopure trialkyne 282, desilylation was affected using TBAF, followed by ruthenium-catalyzed cycloisomerization [214] and cleavage of the chiral auxiliary to obtain tetracycle 283. The carboxylic acid was converted into the corresponding acyl chloride, followed by addition of diazomethane and subsequent Arndt–Eistert homologation [215] to obtain methyl ester 284. Claisen condensation furnished the intermediate β-cyano-ketone, which was subjected to diazotransfer conditions [216] to obtain 285. This compound underwent smooth cyclopropanation with the adjacent benzene moiety to give cis-vinylcyclopropane cyanide 286. Conversion of the ketone to the corresponding triflate followed by mono-reduction of the nitrile furnished cis-vinylcyclopropane carbaldehyde 287, which underwent smooth, but undesired rearrangement to dihydroox-
epin 288. This rearrangement has been observed to be reversible [217]. Treatment with DIBAL-H reduced the carbaldehyde moiety selectively to give alcohol 289. Lactonization was achieved upon Pd-catalyzed CO-insertion to give 290. The desired natural product was obtained after oxidation of the tetrahydrofuran to the desired natural product salvileucalin B (292) using chromium trioxide·3,5-dimethylpyrazole [218].

Oxygen variants overview

The divinyloxirane rearrangement (293 to 294, see Scheme 36) has been investigated in detail by the groups of White and Smith [219, 220]. The synthesis of the cyclization precursors started from enynes like 297, beginning with cis-selective Rieke-Zn reduction. Epoxidation followed by oxidation furnished cis-vinylketone-epoxide 298. Enolate formation and acetate trapping afforded an intermediate enol-acetate, which underwent high-yielding cis-divinylepoxide rearrangement at elevated temperatures to yield dihydrooxepine 299 in good yield. De Meijere and coworkers [221] investigated the selective epoxidation of hexatrienes like 300 to yield cis-divinylepoxide 301. Gentle heating provided bridged bicycle 302, containing two-anti-Bredt olefins in a stereospecific reaction. Doyle and coworkers [222] succeeded in preparing trans-divinylepoxides like 304 via rhodium-catalyzed vinyl-diazo decomposition (using compound 101) and subsequent epoxide formation in the presence of cinnamon aldehyde (303). These rather stable epoxides (see 304) were shown to undergo trans-cis isomerization followed by divinylepoxide rearrange-
ment to give dihydrooxepine 305 at 125 °C. The necessary reaction temperature could be lowered using copper(II) catalysis, accelerating the reaction rate as well.

The vinylepoxide–carbaldehyde rearrangement (295 to 296, see Scheme 37) has been investigated early on by the group of Boeckmann [217]. Dess–Martin periodinane oxidation of diol 306 resulted in a smooth rearrangement at ambient temperature, yielding formyldihydrooxepine 307.

A modified approach has been investigated by the group of Lee, using transition metal mediated diazo decomposition [223]. The in situ generated rhodium-carbenoid formed upon diazo decomposition of 308 underwent cyclopropanation with butadi-
enones like 309. The resulting vinyl-epoxide ketone underwent rearrangement to give dihydrooxepine 310 in good yield. Vinylcyclopropane–cyclopentene rearrangement [13,14] has been shown to be the major competing side reaction in this case.

Nitrogen variants

Three different approaches can be used to incorporate nitrogen into the DVCPR. The cis-divinylaziridine rearrangement (311 to 312, see Scheme 38) after rhodium-catalyzed aziridine formation between vinyl-diazo compound 317 and imine 318 has been found by Doyle [224-226]. Rearrangement occurred smoothly to give desired dihydroazepine 320. Note that the authors suggest a transition state including an opened aziridine zwitterion. Alternatively, a cyclopentylamine can be used in an iminium ion type DVCPR rearrangement (313 to 314, see Scheme 38), or a cyclopropylcarbaldehyde can be condensed with an amine to an imine, which then undergoes the DVCPR rearrangement (315 to 316, see Scheme 38). Müller and coworkers [227,228] investigated the trans-vinylisocyanato–cyclopropyl rearrangement in great detail. Electrocyloversion of initially formed nitrene 321 leads to intermediate 322, which can undergo electrocyclization to give the required trans-vinylisocyanatocyclopropane 323, which underwent the desired rearrangement to give tricycle 324. The group of Boeckman pioneered the heteroatom variants of the DVCPR, namely the vinylcyclopropane carbaldehyde–dihydrooxepine rearrangement [217], the vinylcyclopropane carbimine–dihydroazepine [217] rearrangement and the corresponding cyclobutane analogues [229-231]. A very stunning application [231] has been achieved using the Claisen reaction of dihydroxepine 325 (see Scheme 38) to access vinylcyclopropane carbaldehyde 326, which was in situ converted into the corresponding imine 327 using an aza-Wittig reaction. Subsequent vinylcyclopropane carbimine–dihydroazepine rearrangement furnished cyclic 328 in excellent yield.

Conclusion

The divinylcyclopropane–cycloheptadiene rearrangement has been developed as a versatile method for the construction of seven-membered rings. The utilization in the total synthesis of both sesqui- and diterpenoid natural products as well as in the total synthesis of alkaloids and fatty acid-derived metabolites underlines its robustness and broad applicability. Contribution of the DVCPR as the key step to the solution of some of the most daunting synthetic challenges in present synthetic organic chemistry make it the tool of choice when constrained and highly substituted seven-membered rings are involved. The development of the formal [4 + 3]-cycloaddition (using a tandem cyclopropanation/DVCPR) has largely added to the scope of natural products that were synthesized using a DVCPR and shortened the overall synthetic routes.

Scheme 38: Nitrogen-substituted variants of the divinylcyclopropane rearrangement.
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