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Modern Synthetic Approaches to Cubebene and Related Sesquiterpene Frameworks

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Abstract

Cubebenes and related sesquiterpenes, featuring a tricyclo[4.4.0.0^{1},^{5}]decane framework, exhibit notable structural complexity and diverse bioactivity. This review highlights key synthetic approaches toward these molecules, including diazo-mediated cyclopropanation, metal-catalysed enyne cyclisation, bicycloannulation cascades, and photochemical rearrangements. Mechanistic and stereochemical aspects are discussed, highlighting progress in diastereo- and enantioselective methodologies. Although substantial advances have been achieved, efficient access to higher cubebene analogues remains a synthetic challenge. Integration of bioinspired design, modern synthetic methods, and asymmetric catalysis is expected to further advance concise and stereoselective synthesis of these complex architectures.

Keywords: Asymmetric synthesis, Cyclopropanation, Enyne cyclisation, Sesquiterpenes, Transition-metal catalysis

1. Introduction

Cubebenes were first isolated from *Piper cubera* berries and later also found in several pine species. Natural cubebenes **1-4** and their structural analogues **5-8** (Figure 1)[1,2] represent a distinctive class of sesquiterpenes with the tricyclo[4.4.0.0^{1,5}]decane ring system that have attracted the attention of researchers owing to their diverse biological activities and the unique tricyclic framework.

The synthesis of cubebene analogues holds both practical and academic significance: on one hand, their occurrence in essential oils and reported antimicrobial, anti-inflammatory, and antioxidant properties position them as promising leads for drug discovery and fine chemical applications; on the other, the complex stereochemical architecture of cubebene represents an attractive challenge for the development of efficient synthetic methodologies and strategies for selective functionalisation. Therefore, research on cubebene analogues not only contributes to the understanding of structure–activity relationships within sesquiterpenes but also advances modern approaches in terpene synthesis, catalysis, and molecular design. To date, several total synthesis strategies have been reported for compounds **1-3**.[3,4] However, compounds **4-8** have yet to be made. Herein, we review the general strategies employed for the construction of 6-3-5 ring systems.

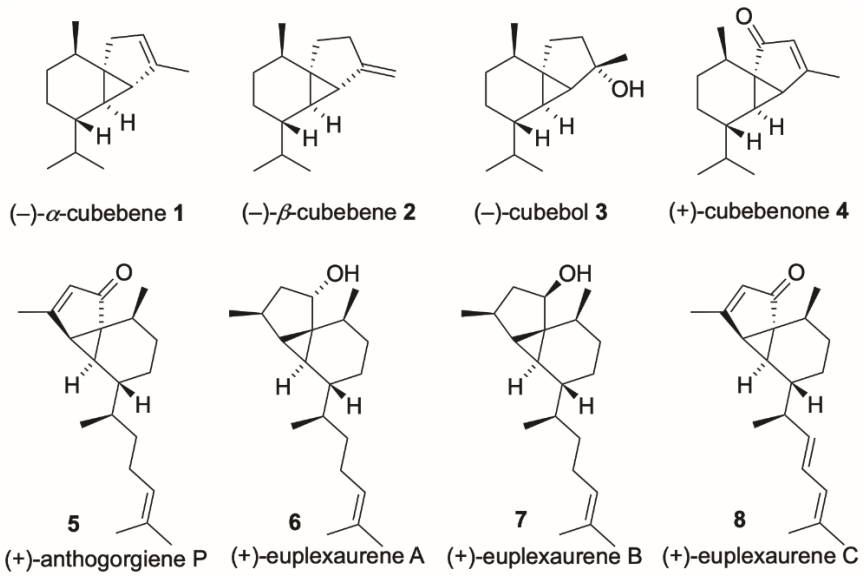
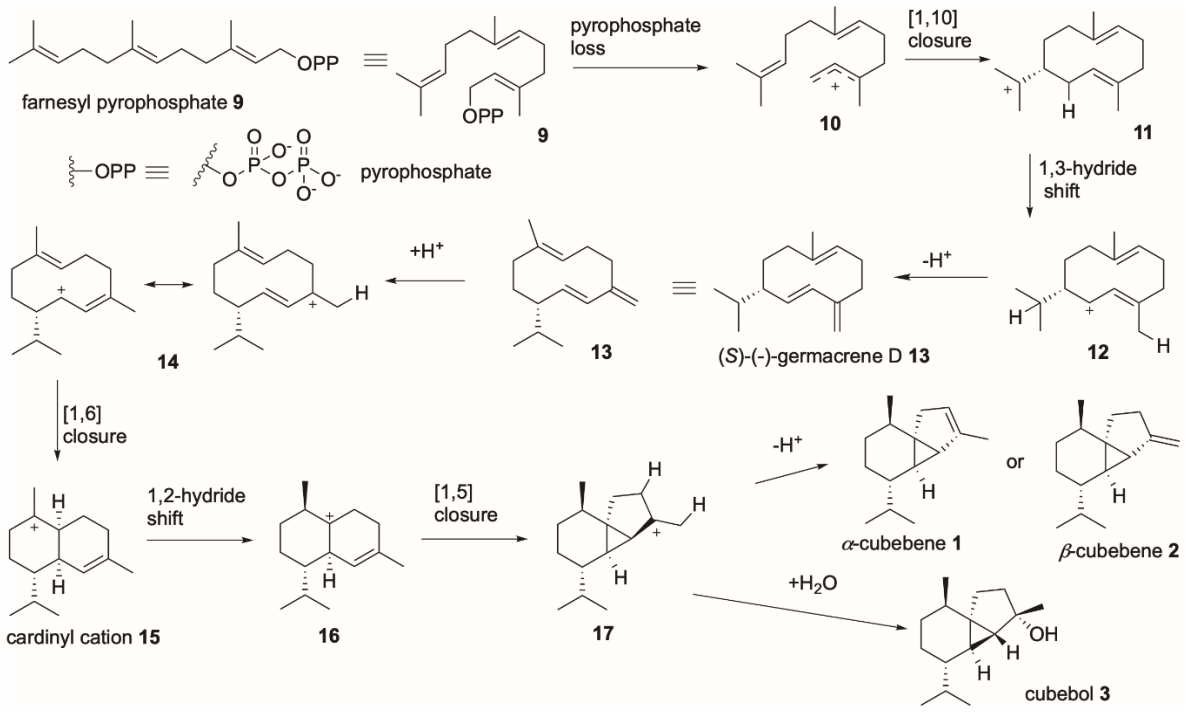


Figure 1. Natural products featuring cubebene tricyclic framework.

2. Synthesis of cubebenes and related scaffolds

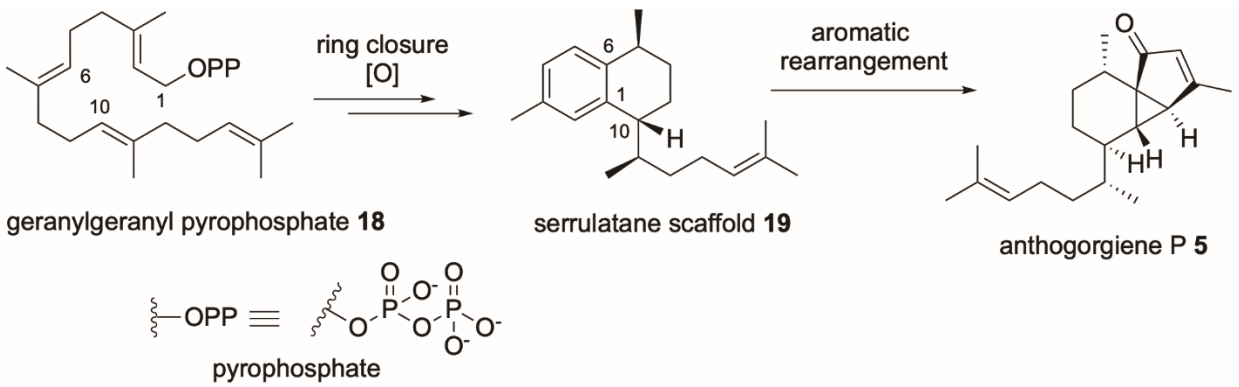
2.1. Biosynthesis

The biosynthesis of cubebene has been studied through deuterium labelling (Scheme 1).[5] Depyrophosphorylation of farnesyl pyrophosphate **9** followed by [1,10] ring closure of cation **10**, 1,3-hydride shift in **11,** and proton elimination frim **12** yields (*S*)-(-)-germacrene D **13** as an intermediate. Protonation of the exo-alkene (**14**) followed by electrophilic [1,6] ring closure gives the cardinyl cation **15**. A 1,2-hydride shift to cation **16** and then a [1,5] ring closure give the 6,3,5-ring system **17**. Then, the outcome depends on the subsequent reactions. Thus, endo-proton elimination gives *α*-cubebene **1**, exo-proton elimination leads to *b*-cubebene **2**, whereas hydrolysis gives rise to cubebol **3**.[5,6]



Scheme 1. Biosynthesis of cubebenes.

For the most recent additions to the cubebene family, the analogues of anthogorgiene P **5**-**8**, biosynthesis has not been elucidated in detail, but a proposed biosynthetic pathway is thought to involve the depyrophosphorylation of geranylgeranyl pyrophosphate **18** followed by ring closure between the C1/C10 and C1/C6, followed by oxidation to the serrulatane scaffold **10** (Scheme 2). The tetrahydronaphthalene is thought to then undergo aromatic rearrangement and oxidation to Anthogorgiene P **5**.[2]

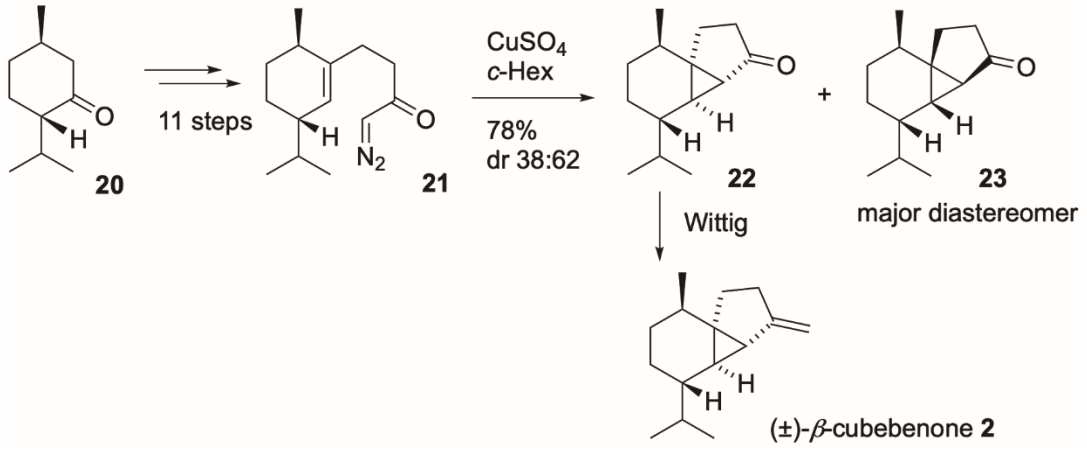


Scheme 2. Proposed biosynthesis of anthogorgiene P.

Over the past 50 years, several methodologies have been developed towards the synthesis of the cubebenes. The typical synthetic strategy involves modifying a cyclic monoterpenoid that can undergo intramolecular cyclopropanation, although there are notable exceptions. In the next sections, we shall survey the reported strategies for the synthesis of cubebene analogues.

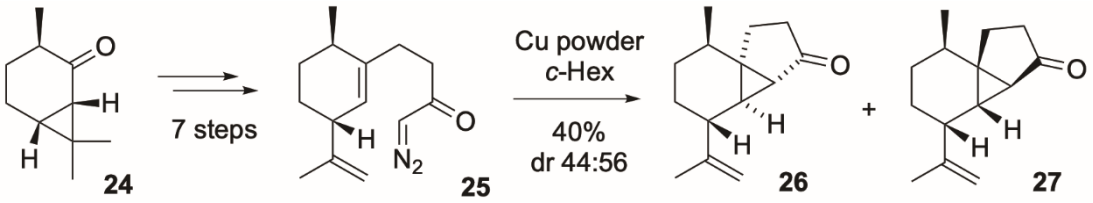
2.2. Diazo-based strategies

In 1969 and 1971, the De Waal group published the first total synthesis of *b*-cubebene **2,** which also constituted a formal synthesis of *a*-cubebene **1** (Scheme 3).[7,8] The synthesis commenced with menthone **20,** yielding within 11 steps a-diazo ketone **21**. The cyclopropanation was performed using stoichiometric amounts of copper(II) sulphate in cyclohexane and afforded a 38:62 mixture of **22** and **23**, respectively, with a 78% combined yield, favouring the unnatural isomer **23**. The practicality of this methodology suffers from poor selectivity and the use of stoichiometric metal salt. However, after isolation, the minor isomer **22** was subjected to Wittig alkenylation to achieve the first total synthesis of *b*-cubebene **2**.



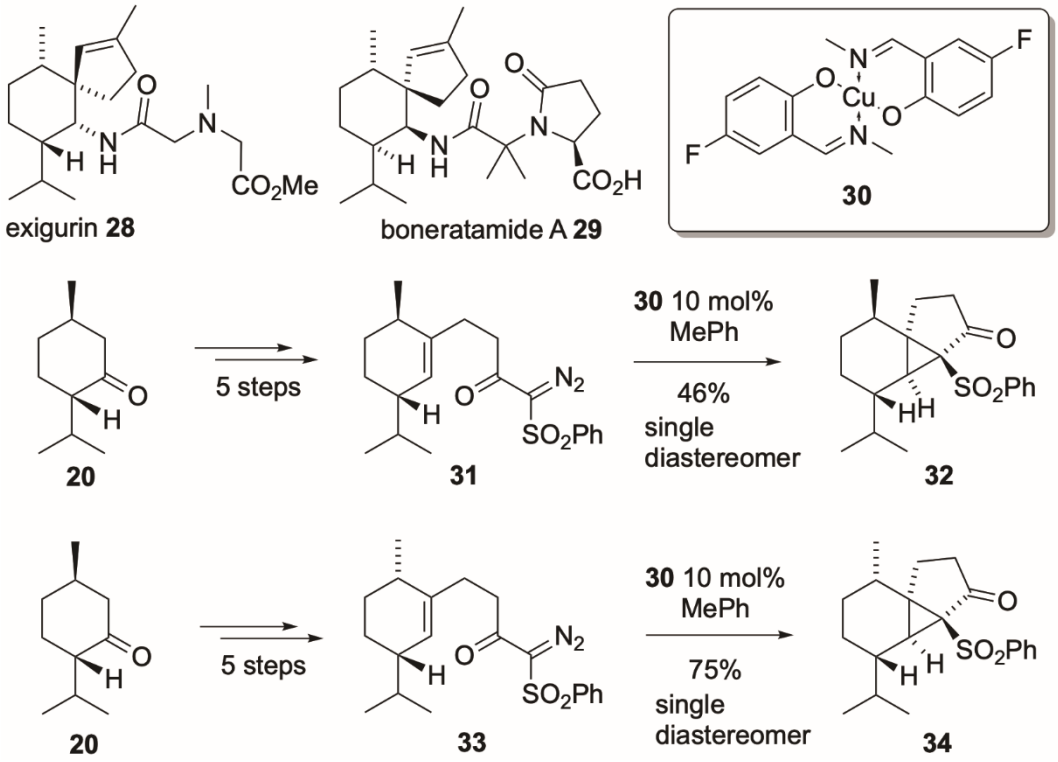
Scheme 3. Key steps of De Waals' synthesis of racemic cubebenes.

The synthetic sequence reported by Yoshikoshi[9] resembles that of De Waals[8] (Scheme 1.4), but has a more efficient synthesis of the key a-diazo ketone intermediate **25**. Starting from (–)-*trans*-caran-2-one **24,** the diazo intermediate was successfully synthesised in 7 steps. The intramolecular cyclopropanation, however, provided a lower yield compared to the De Waals protocol but showed marginally better diastereoselectivity for the desired isomer **26** (dr 44:56)**.** For the stoichiometric copper reagent, Yoshikoshi deployed copper powder instead of copper(II) sulphate. The diastereoselectivity still favoured the cyclopropane being *anti* to the methyl group, as in **27**.



Scheme 4. Key steps of Yoshikoshi's synthesis of cubebenes.

Hosokawa worked on the total synthesis of exigurin **28** and a formal total synthesis of boneratamide A **29** (Scheme 5).[10] Both routes relied on a tricyclo[4.4.0.0^{1,5}]decane intermediates **32** and **34**, analogous to the cubebene nucleus. Similar to the works of De Waal[8] and Yoshikoshi,[9] the synthesis involved intramolecular cyclopropanation of a diazo intermediate. Instead of using an a-diazo ketone, they deployed an *a*-diazo-*b*-keto sulphone. This sulphone was required for the total synthesis but also provided sizeable steric bulk. In this approach, to carry out intramolecular cyclopropanation, stoichiometric copper reagents were replaced by catalytic quantities of complex **30**.

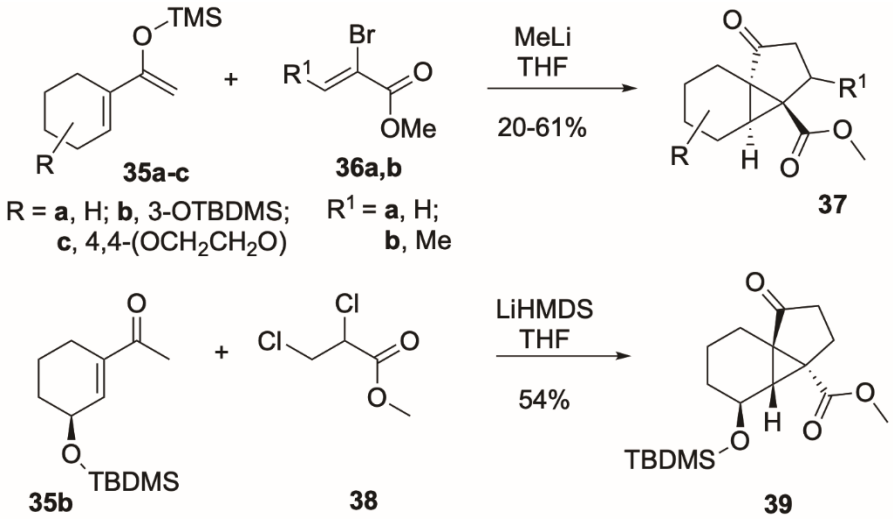


Scheme 5. Key steps in the synthesis of exigurin **28** and bonertamide **A 29**.

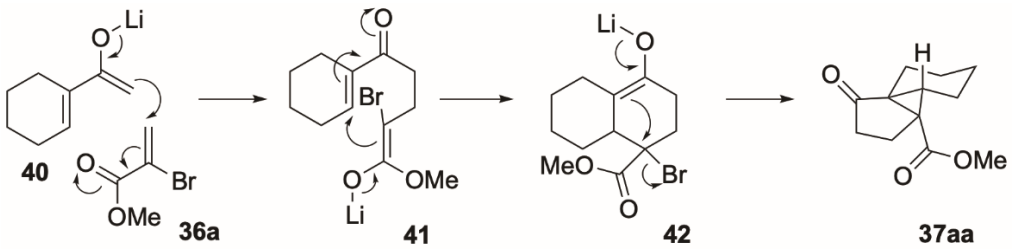
The synthesis of the *a*-diazo-*b*-keto sulphone for both the *anti*-**31** and *syn*-**33** methyl and isopropyl menthone analogues started with menthone **20**. The intermediates were formed in 5 steps each and isolated as single diastereomers. The copper-catalysed intramolecular cyclopropanation proved to be highly diastereoselective for the construction of the tricyclo[4.4.0.0^{1,5}]decane ring system; this was owed to the steric hindrance between the phenyl sulphone and the isopropyl group, enabling high facial selectivity for the cyclopropanation as illustrated by **32** and **34**. For the *syn-a*-diazo-*b*-keto sulphone **33,** the cyclopropanation gave a 75% yield of **34** as a single diastereomer. However, the *anti-a*-diazo-*b*-keto sulphone **31** provided a significantly lower yield of **32**, 46%, but still as a single diastereomer. In both instances, the cyclopropanation installed the cyclopropane on the opposite face to the isopropyl group.

2.3. Bicycloannulation

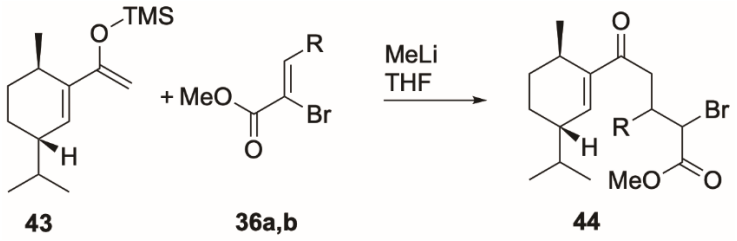
Hagiwara[11–13] developed a bicycloannulation of 3-OTMS 1,3-dienes **35a-c** with methyl 2-bromopropenoates **36,** which undergo a cascade of two Michael additions and terminate with a substitution giving cyclopropanes within a tricyclic system **37** (Scheme 6). The reaction is initiated with the formation of the kinetic lithium enolate generated upon treatment of **36a** with MeLi. The reaction required the use of the silyl enol ether because the generation of the enolate from the ketone with LDA provided no yield in the reaction. Another version of this methodology employed unsaturated enone **35b** and methyl 2,3-dichloropropenoate **38**.[13] In this modification, the lithium enolate and methyl 2-chloropropenoate are generated in situ with LiHMDS; it provides higher yields and does not require the generation of a Michael acceptor ex-situ nor conversion of the enone to the silyl enol ether. Mechanistically, the reaction goes through a stepwise Michael-Michael cascade rather than a [4+2] cycloaddition (Scheme 7). The initial intermolecular Michael addition of **40** to **36a** generated the second enolate **41** that undergoes an intramolecular Michael addition to form **42,** and the cascade terminates with the final enolate undergoing substitution of the bromide yielding the tricyclic system **37aa**. The facial selectivity of the intramolecular Michael addition and sequential ring closure can be controlled by the stereocenter on C-3 on the cyclohexene ring, as in **35b**, which can inhibit the *syn* facial approach of the second Michael addition and drive the formation of an *anti*-conformation of the C-3 substituent and cyclopropane **39**. When this methodology was applied in the total synthesis of cubebene with silylenol ether **43,** there was no conversion to the desired scaffold. The only recovered product was an intermediate from the initial Michael addition **44,** at which the cascade was terminated (Scheme 8).



Scheme 6. Bicycloannulation cascade.



Scheme 7. Proposed mechanistic pathway for the bicycloannulation cascade.

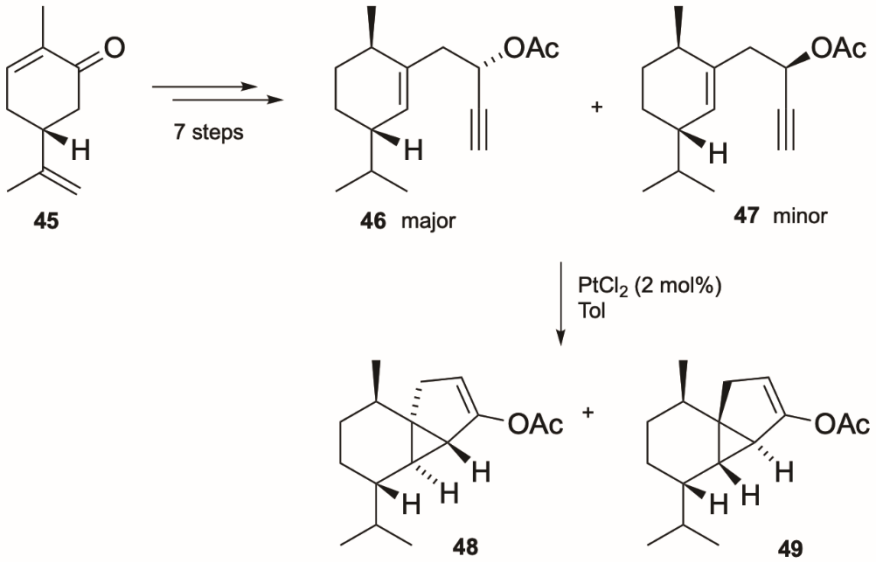


Scheme 8. Unsuccessful attempt at a synthesis of the cubebene scaffold.

2.4. Enyne cyclisation strategies

This is the group of the most successful strategies, where the formation of the cyclopropane ring relies on 1,5-enyne cyclisation catalysed by transition metals of 10-11 groups.

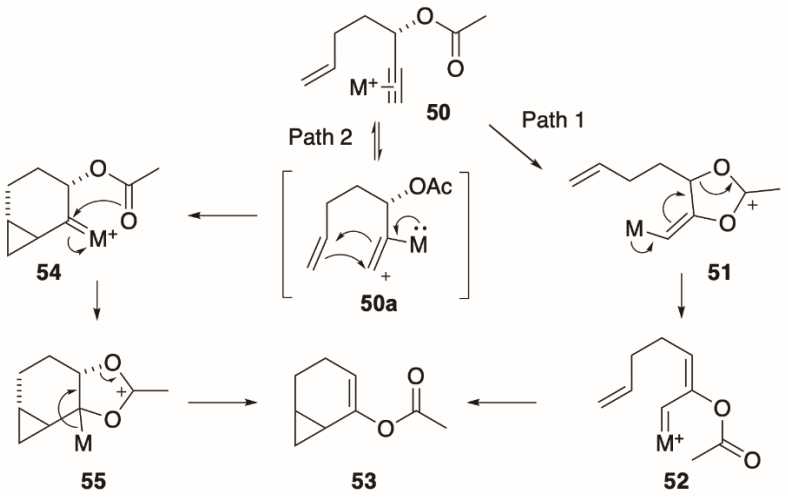
The synthesis by the Furstner group[14] commenced with (*R*)-(–)-carvone **45,** and in 7 steps produced a mixture of two diastereoisomeric acetates, (*S*)-**46** and (*R*)-**47** (dr 63:35)**,** with strategically positioned double and triple bonds (Scheme 9). The key step in the synthesis was a platinum(II) chloride-catalysed cyclopropanation. Importantly, the (*S*)-enantiomer **46** gave the desired product **48** in 92% yield as a single diastereomer. At the same time, cyclisation of the (*R*)-enantiomer **47** under the same conditions proceeded with a lower yield of 79% and with a complete lack of diastereoselectivity to afford a 50:50 mixture **of 48** and **49**.



Scheme 9. Key steps in Furstner's synthesis of cubebene.[14]

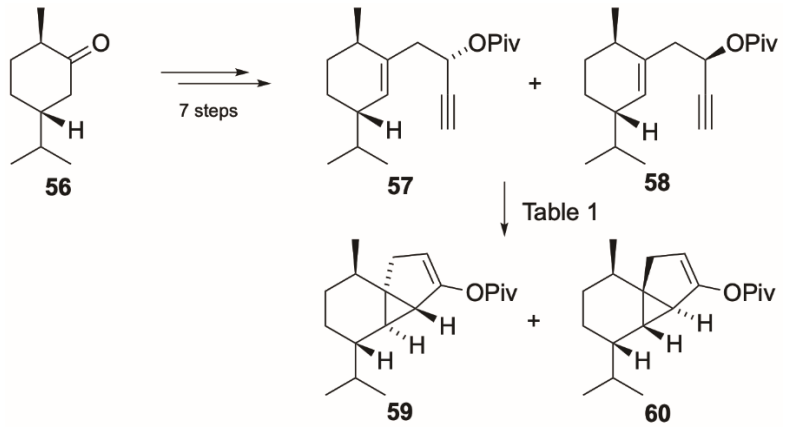
Mechanistically, the high selectivity with (*S*)-enantiomer **46** and the lack of selectivity with the (*R*)-enantiomer **47** prompt an important query (Scheme 10). The dramatic difference in selectivity

suggests that at least 2 potential mechanisms might be in operation.[14,15] In path 1, the propargyl acetate **50** promotes the formation of platinum carbene **52** through a rearrangement of vinyl acetate **51**. The carbene **52** can then undergo cyclopropanation with the tethered olefin to give the cyclopropane product **53.** In path 2, the tethered olefin undergoes electrophilic attack on the activated alkyne to form an intermediate cation **50a**, followed by ring closure to the cyclopropane **54**. The resultant platinum carbene then promotes the acetate rearrangement through the dioxolane cation **55** and platinum elimination to give the target vinyl acetate **53.** Of the two mechanistic pathways, the high selectivity of the (*S*)-enantiomer **46** suggests it goes through path 2 due to the non-planarised acetate group inducing stereo control. In contrast, the lack of any selectivity for the (*R*)-enantiomer **47** suggests that path 1 could play a role, due to the planarisation of the acetate group. Computational mechanistic studies have shown that path 2 is generally energetically more preferred and that the mechanistic pathway is substrate-dependent.[15]



Scheme 10. Possible mechanistic pathways for cyclopropanation using propargyl acetate.

Synthesis of cubebol **3** by Fehr[16,17] has the same key step as in Furstner's[14] route. However, the synthesis of the 1,5-enyne was achieved using tetrahydrocarvone **56,** and a pivalate was used in place of an acetate (Scheme 11). The protected propargylic alcohols **57** and **58** were obtained as an 88:12 mixture, but the two isomers were separated chromatographically. An investigation was conducted into the influence of the catalyst and the stereochemical purity of the 1,5-enyne on the reaction selectivity (Table 1).



Scheme 11. Acyl promoted metal-catalysed cyclopropanation of 1,5-enyne.[17]

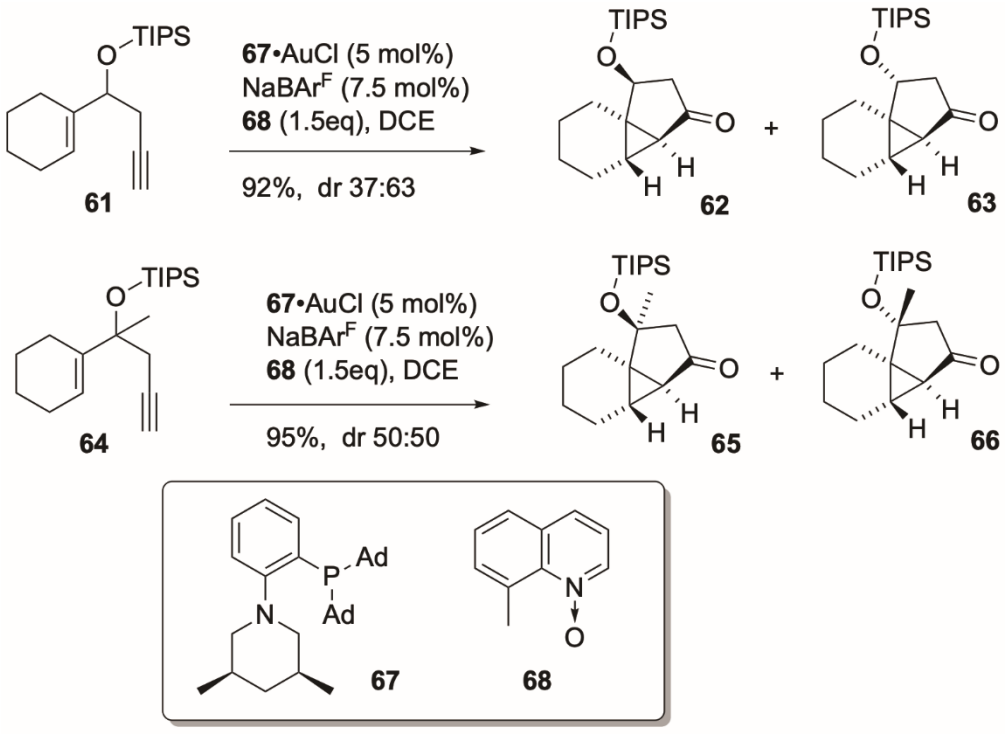
Table 1. Metal-catalysed cyclopropanation of 1,5-enynes **57** and **58**.

Entry	**57:58**	Conditions	**59:60**	Yield [%]
1	9:91	$PtCl_2$ (2 mol%), DCE, 70°C, 9h	60:40	80
2	9:91	$AgSbF_6/AuCl(PPh_3)$ (2 mol%), DCM, RT, 40min	47:53	65
3	70:30	$PtCl_2$ (2 mol%), DCE, 70°C, 9h	86:14	-[a]
4	88:12	$PtCl_2$ (2 mol%), DCE, 70°C, 9h	94:6	81
5	98:2	$PtCl_2$ (2 mol%), DCE, 70°C, 9h	99:1	-[a]
6	98:2	$Cu(CH_3CN)_4BF_4$ (2 mol%), PhMe, 60°C, 9h	99:1	77

[a]Not determined

The use of Pt(II) chloride mirrored the results observed by Furstner[14,] confirming that **57** showed high selectivity and **58** was non-selective (Table 1, entries 1,3-5). $Au(PPh_3)SbF_6$ and $Cu(CH_3CN)_4BF_4$ were tested as alternative catalysts, where the Au(I) provided a lower yield and little selectivity (Table 1, entry 2), whereas the Cu(I) catalyst behaved similarly to Pt(II) but in slightly lower yield (Table 1, entry 6).

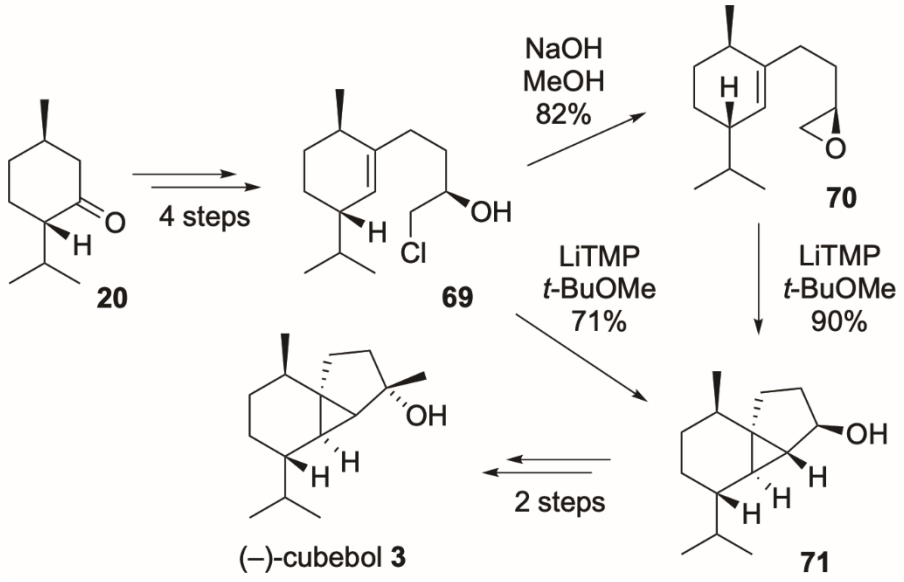
A method for the formation of cyclopropanes from 1,5-enynes catalysed by Au(I) complexes was reported by the group of Ji[18,19] (Scheme 12). They employed *P,N*-ligand **67** and 8-methyl quinoline *N*-oxide **68** as an external oxidant. In this work, two examples of a tricyclo[4.4.0.0^{1,5}]decane ring system were reported. The methodology provides a high-yielding access to tricylco[4.4.0.0^{1,5}]decanes. However, diastereoselectivity remained poor. Compounds **62** and **63** were obtained in 92% combined yield as a 37:63 mixture from the TIPS-protected homopropargyl alcohol **61**. Quaternisation of the alcoholic centre, as in **64**, gave rise to compounds **65** and **66** in a 95% yield with no diastereoselectivity. Additionally, the effect of the conformational rigidity of the amine in the ligand was investigated. Steric interaction between the *cis* dimethyl groups in ligand **67** prevents *N*-inversion, making the non-bonded sp^3 orbital of the nitrogen more accessible to cationic gold species.[18]



Scheme 12. *N*-oxide promoted Au(I)-catalysed cyclopropanation of 1,5-enyne[18]

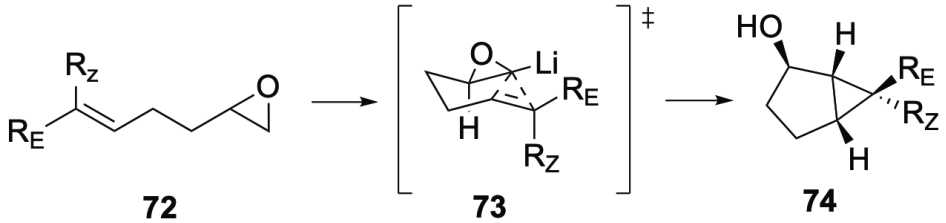
2.5. Miscellaneous strategies

Hodgson reported a 7-step total synthesis of cubebol **3** and, by extension, a formal total synthesis of *a*-cubebene **1** and *b*-cubebene **2**.[20] The key step involved a stereospecific lithium amide-induced cyclopropanation of a bishomoallyic epoxide. When either chlorohydrin **69** or epoxide **70** were exposed to LiTMP, there was an efficient transformation to the tricyclo[4.4.0.0^{1,5}]decane nucleus of cubebene **71,** which in another two steps was converted to (–)-cubebol **3** (Scheme 13).



Scheme 13. Key steps in Hodgson's synthesis of cubebol **3**.[20]

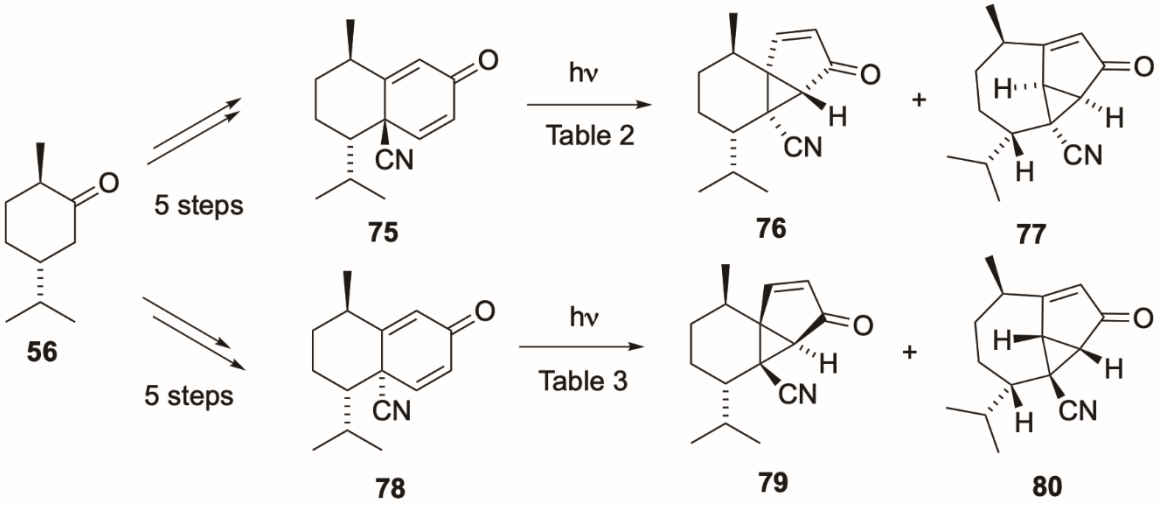
The stereoselectivity of this reaction strongly depends on the absolute configuration of the epoxide and the *cis* or *trans* configuration of the alkene. Mechanistically, the lithium amide deprotonates the terminal epoxide **72**, which then forms a chair-like transition state **73** where the epoxide lies equatorially, making the *cis* substituent on the alkene sit axially and the *trans* substituent lies equatorially. With this method, the alcohol always sits *anti* to the cyclopropane ring in **74**. When diastereomerically pure epoxide **72** is used, an efficient chirality transfer in **73** results in a single stereoisomer of the alcoholic bicyclo[3.1.0]hexane ring system (Scheme 14).



Scheme 14. Stereochemical course of the cyclopropanation of bishomoallylic epoxides.

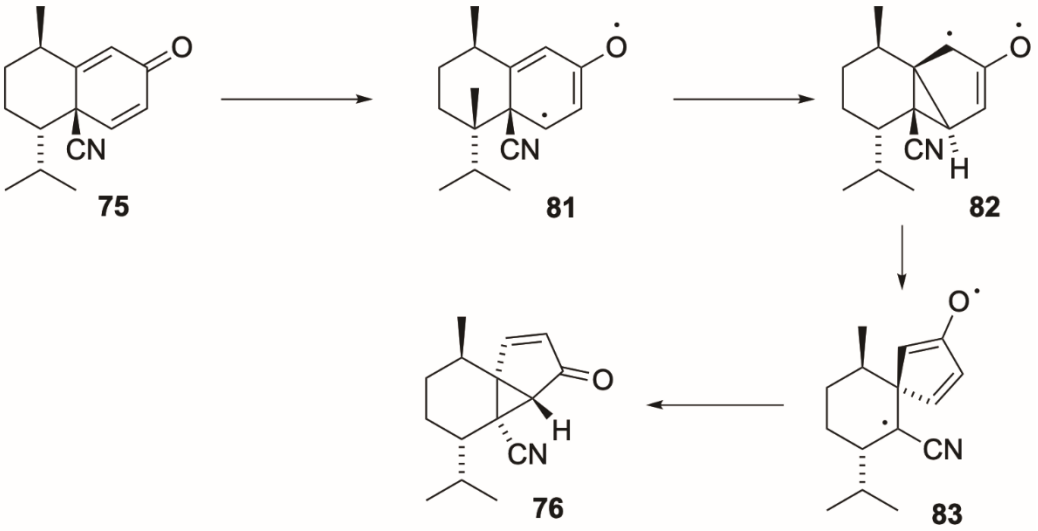
Derksen[21] reported a method for a photochemical 1,4-sigmatropic rearrangement of the diastereomeric divinyl ketone species **75** and **78**, based on earlier literature precedents.[22] Both of these compounds can be prepared in 5 steps from tetrahydrocarvone **56**. In this photochemical rearrangement, the stereoselectivity is determined by the configuration of the cyano-group in the diastereomers **75** and **78**. Under UV irradiation, **75** was converted to tricyclo[4.4.0.0^{1,5}]decane **76** as well as a tricyclo[4.3.1.0^{2,10}]decane ring system **77**. Notably, **76** features the tricyclic system as found

in cubebene with the *syn* arrangement of the methyl and the cyclopropane**.** Unfortunately, the rearrangement of **75** heavily favours the unwanted tricyclic system **77** with the highest ratio of 18:82 for **76** and **77**, respectively (Table 2). Stereoisomer **78** showed increased preference towards **79** with a 91:9 ratio of **79** and **80** (Table 3). For obtaining cubebene scaffolds **76** and **79,** the best results were observed using UV-C light, 235-280 nm, see Table 2, entries 10-11, and Table 3, entries 8-9.



Scheme 15. Photochemical rearrangement for the synthesis of tricyclodecane ring systems.

The computational studies on the mechanism of the photochemical rearrangement revealed that the initial step involves excitation of the a,b-unsaturated ketone **75,** giving the allylic enol diradical **81**, which can then undergo ring closure, forming the cyclopropane diradical **82**, followed by ring cleavage of the cyclopropane, forming the spirocyclic a-cyano enolic diradical **83.** The reaction then terminates through ring closure between the radicals, giving stereospecifically tricyclo[4.4.0.0^{1,5}]decane ring system **76**. The reaction provides complete chirality transfer, but unfortunately, the poor conversion and selectivity for the cubebene nucleus **76** means that it would be an inefficient key step for the total synthesis of cubebene (Scheme 16).



Scheme 16. Proposed mechanistic pathway for the photochemical rearrangement.

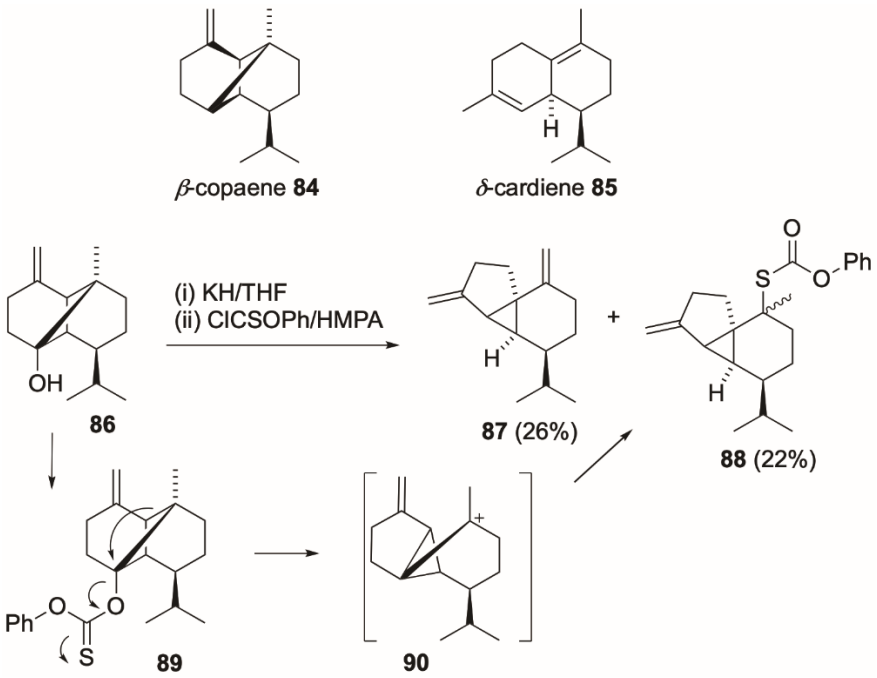
Table 2. Photochemical rearrangement of **75**.

Entry	Light	Time (h)	**76:77**
1	Visible	100	0:100
2	UV-A	2	0:100
3	UV-B	2	0:100
4	Visible	20	10:90
5	Visible	44	5:95
6	Visible	80	0:100
7	UV-A	3	0:100
8	UV-A	9	0:100
9	UV-B	2	9:91
10	UV-C	0.8	18:82
11	UV-C	3	18:82

Table 3. Photochemical rearrangement of **78**.

Entry	Light	Time (h)	**79:80**
1	Visible	24	66:34
2	UV-A	0.5	66:34
3	UV-B	2	75:25
4	UV-B	4	75:25
5	Visible	2	80:20
6	UV-A	2	75:25
7	UV-B	2	75:25
8	UV-C	0.7	91:9
9	UV-C	2	91:9

While working on the total synthesis of *b*-copaene **84,** Wenkert[23] discovered a cationic ring contraction of the copaene skeleton leading to the tricyclic cubebene scaffold (Scheme 17).



Scheme 17. Ring contraction of copaenol **86**, yielding the 6,3,5-tricyclic ring system.

When alcohol **86** was converted into a leaving group, *O*-phenyl carbonothioate **89**, the cyclobutene underwent spontaneous ring contraction, the resultant cation could then either promote a-proton elimination to **87** or undergo trapping of the residual *O*-phenyl thiocarbonate **88**. An attempt has been made to synthesize *b*-cubebene **2** by desulphurisation of **88** with Raney nickel, but this led to further skeletal rearrangement to *d*-cadiene **85**.

3. Discussion

The synthetic efforts towards cubebene and related sesquiterpenes demonstrate the challenges of constructing compact, highly strained carbocyclic frameworks while maintaining control of stereochemistry. The evolution of synthetic methodologies in this area reflects the existing trends in terpene synthesis, moving from long sequences relying on stoichiometric reagents toward catalytic, mechanistically informed strategies.

Cyclopropanations using diazo compounds, pioneered by De Waal and Yoshikoshi, provided the first practical access to cubebene frameworks and demonstrated the fundamental feasibility of constructing the desired tricyclic core. However, these methods suffer from low efficiency, the need for stoichiometric metal salts, and modest diastereoselectivity. Subsequent modifications using α-diazo-β-ketosulfones improved stereocontrol, taking advantage of steric constraints; however, they remain limited by the substrate scope and the challenges of handling diazo precursors.

Transition-metal-catalysed 1,5-enyne cyclisations represented a conceptual breakthrough, offering catalytic, high-yielding routes with improved stereochemical fidelity. Platinum(II)- and copper(I)-mediated reactions displayed good diastereoselectivity, as exemplified by the work of Fürstner and Fehr, whereas gold(I) catalysis provided complementary reactivity under milder reaction conditions. Nevertheless, the mechanistic dichotomy between carbene-type and electrophilic pathways makes it difficult to predict the stereochemical outcome, and there are only limited enantioselective variants of these processes.

Alternative approaches, such as multistep bicycloannulation cascades, photochemical sigmatropic rearrangements, and cationic ring contractions, further expand the synthetic toolbox but remain context-specific. For example, photochemical transformations, though elegant and mechanistically intriguing, often deliver mixtures of rearranged products with limited synthetic utility. Cationic rearrangements of some terpene scaffolds offer access to the desired tricyclic core, but their lack of selectivity and sensitivity to even minute variation of electronic effects hinder general application.

Overall, even with the advanced methodological diversity, achieving a unified, enantioselective, and scalable synthesis of higher cubebene analogues remains a challenging task. Advances in asymmetric catalysis, photoredox activation, and computationally informed synthetic design are expected to narrow the gap between conceptual innovation and synthetic practicality.

4. Conclusions

The synthesis of cubebene and its analogues continues to attract the attention of researchers as a benchmark for innovative synthetic development in terpene chemistry, serving as a testing ground for new catalytic, stereochemical methodologies, and mechanistic insights. While classical diazo-based intramolecular cyclopropanations pioneered by De Waal and Yoshikoshi laid the foundational strategies, subsequent advances, particularly transition-metal-catalysed enyne cyclisations, have significantly expanded the synthetic toolbox. Each approach provides notable advantages in selectivity, step economy, or mechanistic understanding. However, the total synthesis of higher cubebene analogues (compounds **4**–**8**) remains an open challenge. Future progress will likely depend on integrating bioinspired cascade reactions, modern synthetic methods, and asymmetric catalysis to achieve efficient, stereocontrolled construction of the tricyclo[4.4.0.0^{1,5}]decane framework. These

developments not only promise access to unexplored natural and non-natural cubebene derivatives but also enrich our understanding of the complex natural carbocyclic systems.

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