On the origin of some cubebene derivatives — Diels–Alder adducts and the diene structures of solidago compounds

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Abstract: Two reactions, HCl addition and the thermal and (or) microwave assisted Diels–Alder condensation, were performed on α-cubebene (**1**), a vinylcyclopropane-containing tricyclic sesquiterpene. The diene structures originating from these reactions and from subsequent rearrangements of **1** were identified. The stereochemistry of the resulting adducts was established using mostly 2D high-resolution NMR.

Key words: cubebene, tricyclic terpenes from Solidago Canadensis L, Diels–Alder microwave condensation on vinylcyclopropane system.

Résumé : Le α-cubébène (**1**), un sesquiterpène qui contient une unité vinylcyclopropane, a été soumis à une réaction d'addition de HCl et une de condensation de Diels–Alder thermique à l'aide de microondes. On a identifié les structures diéniques qui trouvent leur origine dans ces réactions et dans les réarrangements subséquents du composé **1**. On a déterminé la stéréochimie des adduits qui en résultent en se basant principalement sur la RMN bidimensionnelle à haute résolution.

Mots-clés : cubébène, terpènes tricycliques provenant de *Solidago Canadensis* L., condensation de Diels–Alder à l'aide de microondes sur un système vinylcyclopropane.

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Introduction

Cyclopropane-containing terpenes are present in many botanical extracts (1). The complex relation between the biological origin of this strained cyclopropane system and its facile rearrangement in vitro complicates the exact structural identification. The cyclopropane system is even more susceptible to rearrangement when in proximity to a double bond, as this often induces diene character (2). If the interactive method of extraction, such as microwave-assisted extraction, is used, the likelihood of such reactions increases yet again (3).

We were interested in elaborating our hypotheses on the possible origin of α-cubebene (**1**), a popular vinylcyclopropane-containing tricyclic sesquiterpene present in several plant extracts (in particular, Solidago Canadensis L) (4). In previous papers, we have already reported on its microwave-induced rearrangement (3).

Our current hypothesis should take into account the predominantly photochemical (hν) mode of these transformations on the plant level, the symmetry-allowed processes relating various diene structures, and their stereochemistry.

For such a system one can consider various possibilities, including a Cope rearrangement (5), a relatively easy vinylcyclopropane-cyclopentene rearrangement (5), and exo–endo double bond isomerization. Finally, the entire system manifests several possible sigmatropic shifts with and without respect to Woodward–Hoffmann formalism because of uncertainty as to the concerted character of these transformations (7). The following hypothesis towards a possible retro-synthesis of **1** can then be elaborated as per Scheme 1.

Scheme 1 suggests that germacrene D (**4**) can be a precursor of tricyclic unsaturated sesquiterpenes such as cubebenes **2**, **5**, etc. It is worth noting that **4** is a naturally abundant

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Dedicated to the memory of Professor Wilfried A. König.

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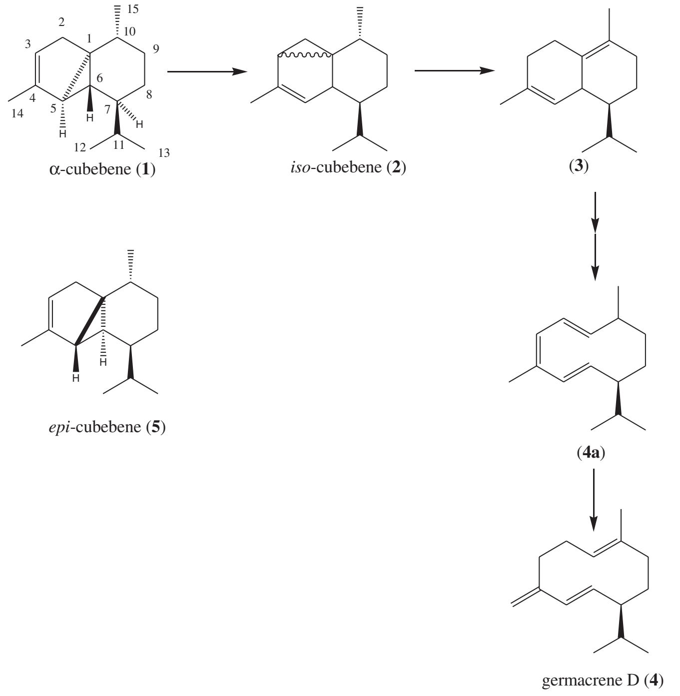
Scheme 1. Possible retro synthetic pathway for the biogenesis of α-cubebene **1**.

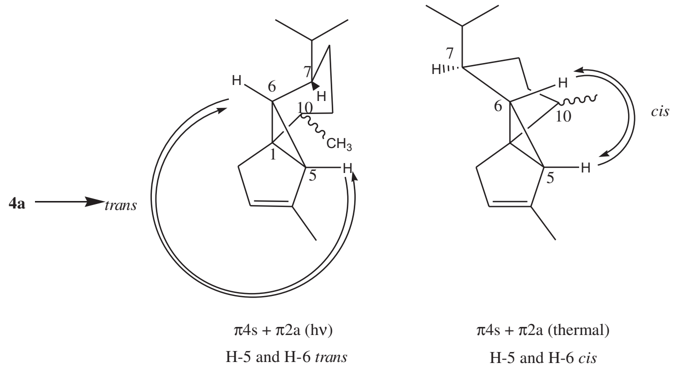


monocyclic sesquiterpene triene, and that like **1**, it has four unsaturations (cycle and three double bonds). It is often present together with natural α-cubebene (**1**) and *epi*-α-cubebene (**5**) as a potential precursor to both. As a part of this transformation it is assumed that **4** enters the isomerization of the double bond from exo to endo position, followed by the shift of the remaining double bond to a more stable conjugated position. One can assume that the rearrangement will then be reduced to a hexatriene-bicyclo[3.1.0]hexene transformation. The bio-originated product will have a geometry conforming to the photochemical pathways of π4s + π2a (Scheme 2) (7, 8) (or of its optical isomer, or both).

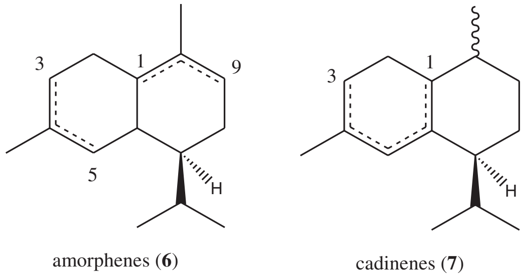
According to Scheme 2, the stereochemistry at the C-10 center is lost because of the non-regioselective H-shift at this carbon. The only remaining stereocenter, C-7 involved, has its isopropyl group β-oriented and is thus a valuable reference point to follow the stereochemistry of these compounds. The value of this hypothesis is reinforced by König transformation (9, 10) of the germacrene D (**4**) into the series of amorphanes (**6**) and closely related cadinenes (**7**) (Scheme 3).

To have the cubebene geometry conform to Scheme 3, H-5 and H-6 should be trans (this is true for both cubebenes and *epi*-cubebenes); as well, H-7 must be trans to H-6 to maintain the voluminous isopropyl group in the equatorial position (Scheme 4). The concerted character of such a photocyclisation, which was suggested by Padwa et al. (11), was subsequently challenged by Seeley (12). If this second hypothesis is retained, steric hindrance should be a driving force of the stereochemistry final product. The isopropyl group should remain in the equatorial position, and the C_1–C_5 bond should be formed through a less hindered pathway.

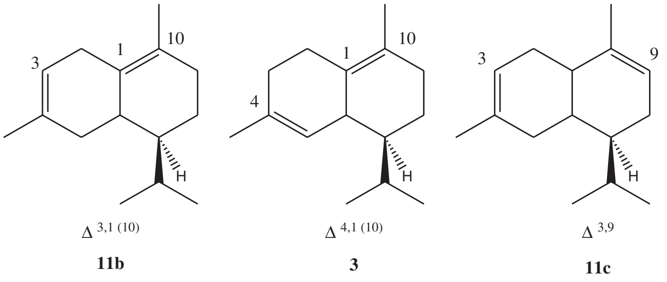
Scheme 2. Differences between thermal or photochemical ring closure leading to **1**.



Scheme 3. Skeleton structures of the amorphenes **6** and cadinenes **7** families.



Scheme 4. The dienes possibly coming from the cyclopropane ring opening of α-cubebene **1** and capable of forming the dichlorinated product **13**.



In such a manner, the hypothesis of formation of cubebene from germacrene D (**4**) via the photochemical pathway in plant could be advanced. Many uncertain points remain open. For example, the second vinylcyclopropane *iso*-cubebene **2** structure could undergo rearrangements leading to more strained structures prior to allowing the formation of either of the two cubebenes by thermal (13) or microwave-assisted conditions (14). Many of the compounds presented in Schemes 1–3 displayed the diene structures. It seems necessary then to show that the dienes are effectively present in these pathways. The best way to confirm this point is to perform two reactions: (*i*) in particular the Diels–Alder addition, enabling the trapping of the diene isomeric structure and the addition of HCl to the double bond and (*ii*) following the opening of the cyclopropane toward olefin, the second addition of HCl (with or without its previous rearrangement because of the carbocation formation).

Results and discussion

Diels–Alder reaction on α-cubebene (1)

As a first step of this study, we performed molecular modelling of many of the dienes discussed here (Scheme 5). The dienes were limited here to those able to produce the homoannular *s-cis*-1,3-diene conformation from the cubebene structure. It is also observed that the cubebenes with the cyclopropane in the C1-C3 position are less stable than those having the cyclopropane in the C1-C5 position. A similar conclusion could be drawn for the monocyclic trienes presented in Scheme 1: the starting triene structure can undergo either the 1,5 sigmatropic shift or the less favoured 1,3 shift; however, germacrene D (**4**) remains among the most stable triene substrates. The most interesting six diene structures **8a**–**8f** were those that originated from the cyclopropane-bearing ring of **1** but were also 1,3-homoannular dienes with their natural s-cis conformation. Incidentally, the molecular modelling of these six diene structures shows that the diene, cadinene-3,5-diene (**8b**), is the most stable of this group of six homoannular dienes.

We chose maleic anhydride as a dienophile because of its proven dienophile character, its solubility, and its easy focalisation under microwave heating. Two different modes of Diels–Alder reaction were performed: thermal and microwave-assisted (MAP and in vessel) (14), and the reactions were monitored using GC-MS, GC, and TLC.

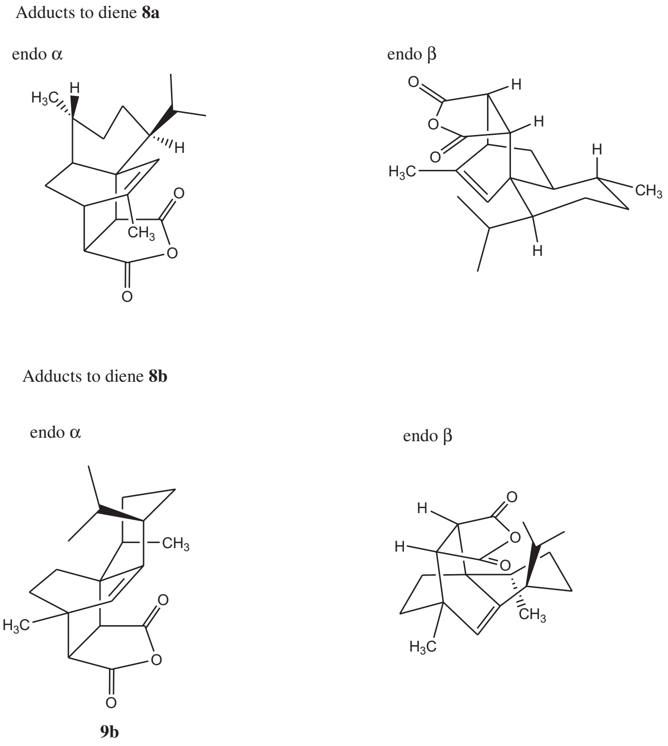
GC-MS revealed the presence of the Diels–Alder adduct at m/z 302, which was obtained by heating substrates at a 1:1 molar ratio in toluene, for variable amounts of time, or by microwave. The yield was optimized at 12% in the thermal reaction; it was up to 23% with microwave heating but only 15% using MAP method (15).

The careful chromatographic isolation of this adduct enabled us to further identify its structure as being **9**, essentially from the 2D NMR evidence. The final adduct structure relative configuration at asymmetric carbons, discussed as being a result of two diastereo differentiating approaches (endo, exo) from two possible sides of the molecule of cubebene **1**, was established from the NOESY experiments performed (Fig. 1). The problem of the structure of the starting diene was again examined at this point.

All six isomeric diene structures **8a**–**8f** (Scheme 5) are *s-cis* homoannular dienes. The most distinctive spectral characteristic of the adducts obtained from these dienes was predicted to be the number of vinylic proton signals and the methyl-15 being attached to sp^2 or to sp^3 carbon C-4. The presence of the signal at 5.73 ppm (doublet 2Hz) for one proton in its 500 MHz spectrum eliminates two of these structures from consideration; the methyl-15 singlet signal was then observed and identified as being attached to the sp^3 quaternary carbon at 1.286 ppm. The isopropyl signal displayed the large non-equivalence of its two methyls (0.90 and 0.75 ppm doublets), indicating the steric hindrance in this crowded structure (16).

These results lead to the conclusion that the adduct structure fitted best the structure of diene **8b** (Scheme 6). Further analyses were then performed, taking into consideration four structures — two possibilities of approaches (resulting in Diels–Alder adducts endo or exo) of the dienophile to diene **8b** — from the alpha or beta side of **1**, with the isopropyl beta orientation in this natural product serving as a reference to the identification of these sides of the molecule.

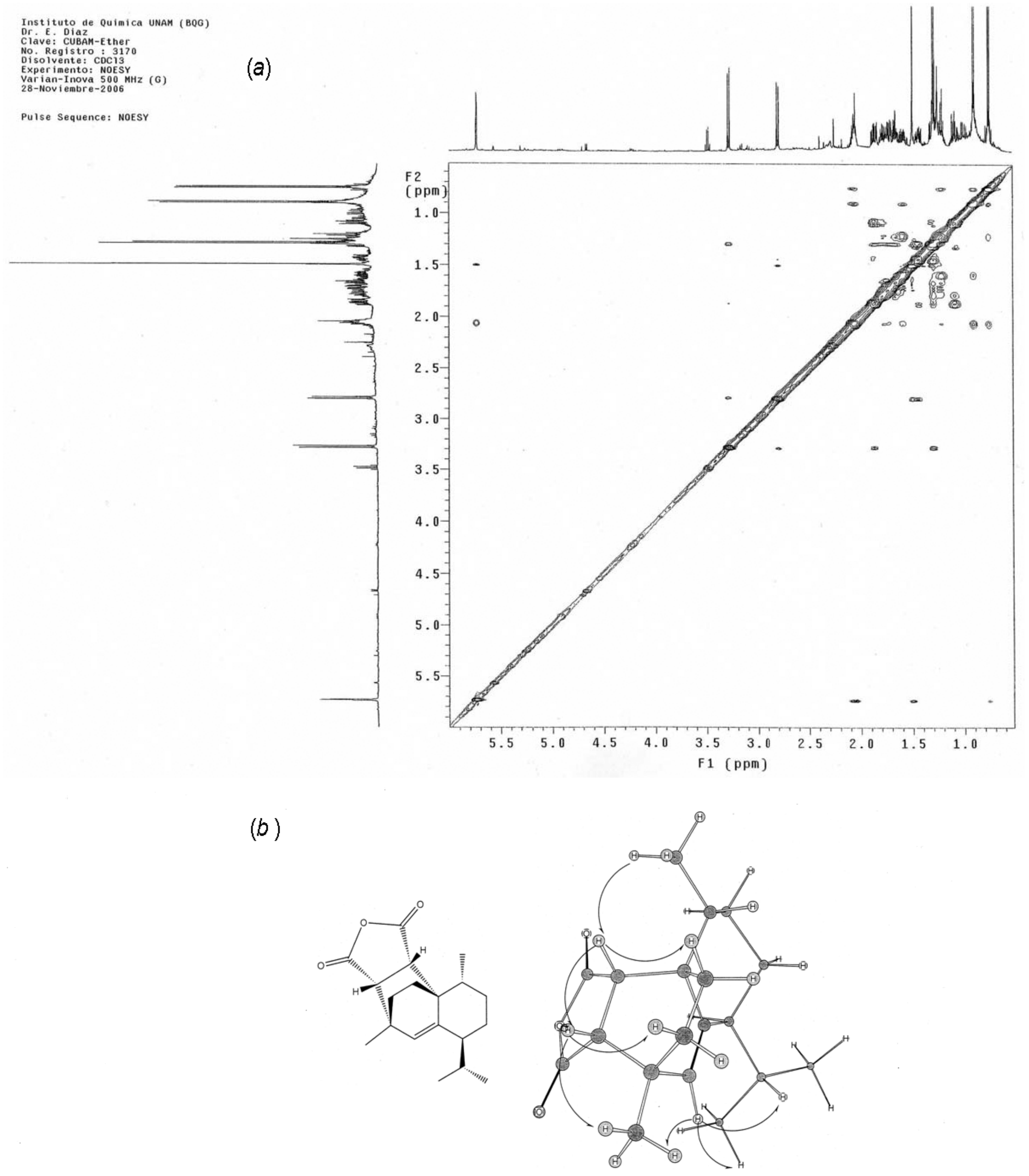
Scheme 5. Structures of the four most likely adducts, as supported by preliminary results.



Molecular modelling indicates that the endo adducts obtained from α (opposite to the isopropyl side of **1**) are more stable than their corresponding exo adducts. The approach from the same side of the isopropyl (β) but according to the endo preference also gives a relatively stable adduct isomer (Scheme 4). The calculated energies of four isomeric structures resulting from the diene **8b** (endo or exo complexes) indicated that for diene **8b**, the adduct endo alpha displayed 55.77 kcal/mol (1 cal = 4.184 J), compared with the second endo beta of 56.53 kcal/mol and to two exo resulting complexes at α 61.29 kcal/mol and β at 58.28 kcal/mol. This difference is also an indication that the presence of a bulky isopropyl group played a direct role in this addition. The reciprocal trans orientation of methyl C-14 and the isopropyl groups should be maintained in this adduct structure and the *endo*-α adduct will, however, have both substituents in equatorial positions. The same analysis was performed for the diene **8a**, which does not lead to the obtained adduct **9**.

To complete the analysis, high-resolution 2D proton NMR experiments were performed. The NOE experiments enabled us to distinguish between these adducts, in particular between endo-α and endo-β, by evaluating the distance between the maleic methine protons and CH$_3$-4, for example, as well as the vinyl proton and three methyls (C-14 and two from the isopropyl group). The complete analysis of H-1 and C-13 is summarized in Table 1. The key element to support the proposed structure was the clean AB pattern for both methines belonging to the maleic anhydride moiety of adduct. The signals at 3.25 and 2.77 ppm (d, J = 9 Hz) show the lack of any additional couplings, which eliminated struc-

Fig. 1. NMR of adduct **9b** NOESY. (*a*) Upper run: 500 MHz ^{1}H spectrum. Lower run: NOESY within 0–6 ppm range. (*b*) Scheme of NOE interactions.



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Instituto de Quimica UNAM (BQG)
Dr. E. Diaz
Clave: CUBAM-Ether
No. Registro : 3170
Disolvente: CDCl3
Experimento: NOESY
Varian-Inova 500 MHz (G)
28-Noviembre-2006

Pulse Sequence: NOESY
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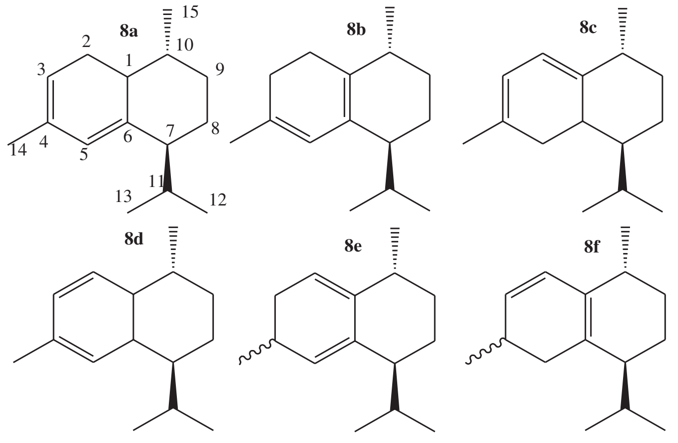
tures of adducts originating from dienes **a**, **d**, **e**, and **f**. The one vinylic proton at 5.73 ppm (d, J = 2 Hz) finally eliminates the structure of adduct arising from diene **8c**. (Fig. 1)

It is worth noting that the cubebene **1** vinylcyclopropane system should undergo a 1,3-sigmatropic shift to form diene **8a** instead of the usually more favoured 1,5-sigmatropic shift that would form diene **8b**. Conversely, assuming that the α-cubebene **1** is first isomerized via the vinylcyclopropane–cyclopentene rearrangement pathway (Scheme 5) to the isomeric cubebene **2** also with the vinylcyclopropane to form the 1,4-diene **8b**, it should undergo 1,3-sigmatropic migration but also a more complex two-step H-migration to

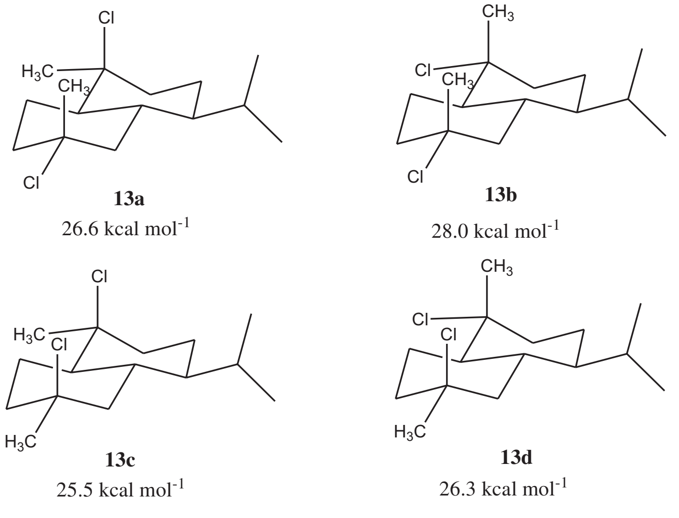
Table 1. Some of the possible dienes resulting from the opening of the cyclopropane and its subsequent rearrangement. These particular dienes are capable of forming Diels–Alder adducts. The table shows energies computed from Hyperchem™ and general information pertinent to each structure that will help identify the adduct formed (1 cal = 4.184 J).



Diene	Position of the double bond	Hybridization of C-15 following adduct formation	Number of vinyl protons in adduct	ΔE (kcal mol^{-1})^a
8a	3,5	sp^2	1	4.23 (H-1,β), 2.66 (H-1,α)
8b	1,4	sp^3	1	0.00
8c	1,3	sp^3	2	7.11
8d	2,4	sp^2	1	7.09 (cis), 6.59 (trans)
8e	1,5	sp^3	0	2.23 (CH$_3$-4,β), –1.49 (CH$_3$-4,α)
8f	2,6	sp^3	1	0.72 (CH$_3$-4,β), 0.3 (CH$_3$-4,α)

[a] Referred to the most stable diene structure **8b**.

Scheme 6. The four stereoisomers of the dihydrochlorinated products **13** and their energies. (1 cal = 4.184 J).



finally achieve the 3,5-diene. Incidentally, the cubebenes **1** and **5** have been found to be more stable than the *iso*-cubebene (**2**) by up to 5 kcal mol^{-1}.

The syntheses of the identical adduct by both thermal and microwave-assisted methods were observed. The difference between endo-β and endo-α approaches to the 1,4-diene (**8b**) is the presence of the bulky isopropyl group, which cannot share space with the relatively large maleic anhydride bridge. The β equatorial orientation of this isopropyl is also an important internal reference point to the identification of the stereochemistry of the entire adduct (absolute configuration **7*S***, **10*R***). The isopropyl-bearing ring of the diene remains, then, the stereo template to follow the regio and stereo specificity of the addition. The final stereochemistry of the adduct **9** can then be proposed as in Scheme 5 and Fig. 1, leading to the structure obtained in agreement to the diene behaviour, following the predictions of both Hirsch (7) and Padwa et al. (11), as far as absolute configuration is concerned. The appealing attempt of the separation of diene **8b** as a result of cubebene **1** rearrangement through heating or MAP modes, as in König's case (9, 10), was unsuccessful, and led instead to a mixture of olefinic compounds. It seems, then, that the maleic anhydride dienophile can be considered as an efficient and specific quencher of this diene among some other dienes.

HCl addition to cubebene (1)

The second attempted reaction was the addition of HCl in methanol solution of α-cubebene (**1**) at 0–5 °C. This was expected to produce the additional evidence for the diene structure discussed in the previous sections through, first, the Markovnikov addition to the 3,4-double bond of the α-cubebene (**1**) followed by an acid-catalyzed rearrangement of its cyclopropane moiety, rearranged through the carbocation pathway (these two reactions could take place in the opposite order). If the elucidation of the addition outcome in the first step is easy, the cyclopropane rearrangement is difficult to predict, especially for the terpenes. The bicyclo[3,1,0]hexene frame could undergo many types of rearrangement under acidic conditions, leading also to the opening of cyclopropane and the formation of dienes. The presence of several potential tertiary carbocations bears witness to this difficulty.

When cubebene (**1**) was treated with a dry HCl saturated methanol solution at 0–5 °C, the major product (25% of yield) displayed the addition of two HCl molecules, as indicated by mass spectrometry. Unambiguous identification of the adduct stereochemistry is, therefore, the best proof of diene structure for **3**.

In the abundant literature on the subject of diene sesquiterpenes, some structures are of particular interest: those of dienes **11**, **9**, **10**, and **12**, the last one characterized by König et al. (9, 10). These dienes, however, were isolated from two completely different Solidago species; although in terpene chemistry the isomerization and rearrangement of the skeleton is relatively frequent, this does not lead to well-defined diene adducts. Diels–Alder reactions on these dienes were not attempted by König, but in 1998 he attempted to isomerize the diene with pTsOH and obtained another stable isomer. Incidentally, four structures with the best fit for the HCl addition product are described in the next section of this paper.

König's heating of this diene revealed an easy shift of the double bond of the structure, with three other dienes being obtained through this isomerization. The production of the Diels–Alder adduct in the case of α-cubebene (**1**) used in this study is thus a chemically formal proof of trapping of the double bond in the 1,3-conjugated *s-cis* homoannular position; however, this diene is isomeric to the one described by König (9, 10).

The NMR spectra (1D and 2D) of the dihydrochlorocubebene adduct product showed that the adduct should have two *trans*-fused rings and that both methyls (C-14 and C-15) are equatorial (meaning that both chlorine atoms were axial, thus confirming the Markovnikov rules). It is generally accepted that in methyl derivatives of cyclohexane, as well as in a terpene field, the equatorial methyl-13 signal displays a chemical shift at 35–37 ppm, at ca. 10 ppm lower field than the axial one (20–23 ppm). The chemical shift in the 1D C^{13} NMR spectrum of compound **13c** shows two methyl signals, identified with help of DEPT experiments as being methyl-5 at 37.8 ppm and methyl-10 at 34.9 ppm. Because of the chemical shift, we can conclude that both methyls are in equatorial positions (17, 18). The 600 MHz spectra (Table 2) and Fig. 2) enabled us to establish the structure of the dichloro derivative as being **13c**, with two chlorine atoms placed on carbons 10 and 4, respectively. Further study of the dihydrochloro adducts **13** was performed with help of molecular modelling of eight possible structures for these dichloro adducts: four in *trans*-fused and four in *cis*-fused decalins. The most stable structures in the two series were those with the quaternary carbons bearing Cl and CH_3 groups (C-4 and C-10) and where both methyls were equatorial **13c**. It is necessary to point out that the presence of the CH_3 and Cl on the same carbon will always lead to one axial substituent contributing to the creation of two gauche interactions (19). When we consider the addition of the first HCl to the molecule under the two-step addition scheme, the original α-cubebene (**1**) double bond position responds well to the dichloro derivative structure. Under the same hypothesis, the second double bond can originate in either of two essentially similar structures: with the double bond in the 1,10/1,14 position or in position 9,10/1,14 where it is unrelated to the cyclopropane moiety.

Table 2. NMR data for adduct **9b** ($CDCl_3$) ^{1}H and ^{13}C.

C No.	δ C	δ H
1	36.5q	—
2	34.0	1.86(ax), 1.09(eq)
3	34.6	1.44(eq), 1.31(ax)
4	29.7q	—
5	128.78	5.73 (d, *J* = 2.0 Hz)
6	147.0q	—
7	45.0	2.06
8	22.3	1.22(eq), 1.58(ax)
9	29.0	1.66(eq), 1.69(ax)
10	38.2	1.82
11	28.0	2.05
12	20.8	0.90
	(a)	
13	17.0	0.75
14	16.9	1.30
15	22.85	1.50
Maleic anhydride moiety		
1a	47.0	3.78 (d, *J* = 9 Hz)
4a	50.9	2.79 (d, *J* = 9 Hz)
Cla-CO	172.18	
C4a-CO	171.7	

Note: ax = axial, eq = equatorial, q = non-protonated carbon, d = doublet.

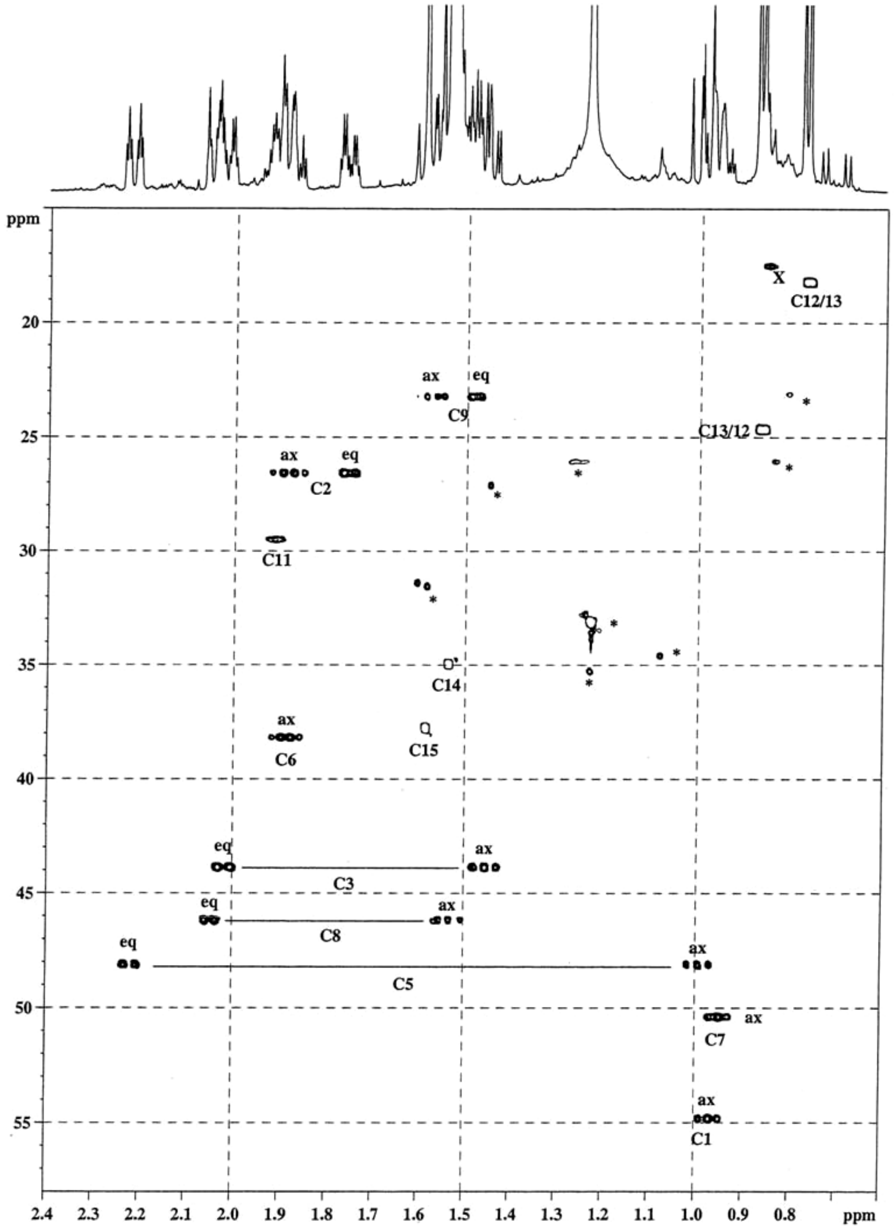
A second hypothesis of formation of the dichloro derivative could also be advanced. The acid catalysis of the cubebene **1** leads to diene **3**, already observed by König et al. (9, 10), which undergo double Markovnikov addition of HCl. Note that this second one-step route leads to the addition of protons from HCl to the carbons C-5 and C-1, instead of to C-3 and C-1 as in the first route. To clarify this point, deuteration with dry DCl in deuterated methanol was attempted. The reaction enabled us to establish the position of deuteration at C-1, C-9, C-3, and C-5. There are then four endocyclic unconjugated dienes with double bonds at -4,9 (**9**), -10,4 (**3**), -3,1, and -3,9, which can produce the Markovnikov's dihydrochloro adduct corresponding to the one identified in this work. The presence of exocyclic double bond dienes was turned down because of the absence of exocyclic methylene signals in the NMR proton spectra of this series. The fact that many amorphenes were identified in some extracts can be asserted by the deuteration (9, 20).

Because of the identification of reduced intensity of proton chemical shifts corresponding to the H-3, H-5, and H-9 in HSQC experiments on the DCl adduct, we concluded that the diene structures were one or many of the followings **3**, **11a–11c**.

Conclusion

The Diels–Alder adduct stereochemistry identification is an interesting attempt to show the corresponding isomeric diene presence within the very complex scheme for cubebene isomerization. The diene structure is then deduced from the adduct structural features. The stereochemistry of this adduct was established in a satisfactory manner con-

Fig. 2. NMR of dichloro derivative **13c** HSQC (600 MHz).



forming to the cycloaddition rules: the dienophile comes from the less hindered side of the diene to form the adduct. These results are reinforced by the molecular modelling calculations.

It is then assumed that the hydrochlorination of **1** proceeded via the formation of the protonated species, which is rearranged to the more stable of two possible carbocations leading to the Markovnikov addition as a final result.

Unfortunately, there are at least four possible diene structures that fit the HCl addition to the double bond: both vinylic carbons have the same substitution level but not the same access to the double bond for the bulky Cl^- ion.

More interestingly, to give such a dichloro adduct, the diene should have its double bond placed in, for example, -3,4 and -1,10 positions. This means that no single one of these dienes is able to produce the Diels–Alder addition described in this study. König's heating experiments revealed an easy shift of the double bond of the diene structure. The production of the Diels–Alder adduct in the case of α-cubebene (**1**) used in this study is thus a chemically formal proof of the quenching of the double bond in the 1,3-conjugated *s-cis* homo annular position; however, this diene is isomeric to the one described by König (9, 10).

The isomerization of the vinylcyclopropane to cyclopentene and the shift of the original double bond of cubebene both took place. In such a manner, the easy epimerisation of cubebene under microwave conditions is justified.

Once the dienes have been obtained, they can be further rearranged into those that are Diels–Alder precursors. In this respect, this diene is more stable since it is homonuclear and 1,3-conjugated and has natural *s-cis* conformation. For this purpose, the formal identification of the Diels–Alder adduct with maleic anhydride is very symptomatic. Both reactions,

Table 3. NMR data for dichloro derivative **13c** ($CDCl_3$) H-1 and C-13.

C No.	δ C	δ H
1	55.0	0.97(ax)
2	26.5	1.74(eq), 1.87(ax)
3	43.6	1.44(ax), 2.03(eq)
4	74.8(q)	—
5	48.1	0.99(ax), 2.23(eq)
6	38.2	1.87(ax)
7	50.3	0.945(ax)
8	46.2	1.53(eq), 2.06(ax)
9	23.2	1.49(eq), 1.575(ax)
10	78.0(q)	—
11	29.5	1.92
Methyls		
12	18.7	0.76[a]
13	24.8	0.88[a]
14	34.9	1.53
15	37.8	1.58(s)

Note: q = non-protonated carbon, s = singlet, ax = axial, eq = equatorial.

[a] Assignment can be inversed.

Table 4. NMR of partial deuteration experiment in **13c** synthesis.

Double bond position	D position in ^{1}H NMR	Proton suppression
-4,9 **11a**	d5, d9	0.99(H-5ax), 1.575(H-9ax)
–10,4 **3**	d1, d5	0.97(H-1), 0.99(H-5ax)
–3,10 **11b**	d1, d3	0.97(H-1), 1.44(H-3ax)
–3,9 **11c**	d3, d9	1.44(H-3ax), 1.575(H-9ax)

Diels–Alder and the addition of HCl, proceeded by several stepwise mechanisms. In such a manner, the respecting or not of the Woodward–Hoffmann formalism for the Diels–Alder adduct stereochemistry should then be considered as accidental.

Incidentally, the structure of the dihydrochloro adduct **13c** (Tables 3 and 4) is different than those described by, for example Burk (21) and Piers (22); as well, it has a different isopropyl orientation. X-ray analysis of the equivalent dihydrohalo structures also displays such a differently oriented isopropyl (23).

It is thus concluded that the cubebenes **1** and **3** with their original cyclopropyl–vinyl system can isomerize to many dienes: to 1,3- conjugated or to several deconjugated ones. The first is able to produce the Diels–Alder adduct and the second system produces the addition of two HCl.

When considering the -1,2 and -1,10 double bond containing intermediates, it is also possible to assume that their spontaneous reaction should go in the direction of the cubenol, leaving the hydroxyl group on the angular C-1 position (3) as observed in our previous paper when reacting **1** with methanol/HCl (3, 24).

The results of this deuterium labelling should be interpreted cautiously because of the sigmatropic shifts possible in this system and because of, as usual, the partial and relatively low yield of this reaction.

Experimental

General

All chemicals, solvents, chromatographic materials, and deuterated solvents were purchased from Sigma-Aldrich Chemicals (USA). The cubebene sample was obtained from Solidago Canadensis L as described in ref. 3 and the pure samples of compound **1** were also purchased from Sigma-Aldrich Chemicals.

NMR spectroscopy

NMR 1D experiments were performed using a Varian Inova spectrometer at 500 MHz for proton and 125 MHz for carbon-13 and a Bruker AMX at 600 MHz for proton and 125 MHz for carbon-13, respectively. In all cases the samples recorded at 295 K were prepared in $CDCl_3$ (dimethylsulfoxide-d_6) ca. 10% solution at 25 °C; chemical shifts were referred to the TMS or referenced to a residual signal of chloroform at 7.24 ppm. Selected 2D experiments were run using a standard Varian package of Inova programs for COSY and NOESY. For HSQC experiments, the Inova program for short range coupling (less than 140 Hz for 1*J* Hz) was used. The long range proton–carbon experiments (HMBC) were recorded with a Varian Inova pulse program, optimized for long range couplings (3*J* C, H 9.0 Hz). A DQF-COSY spectrum (25) was collected on a 800 × 1024 data matrix and the TOCSY spectrum was collected with a mixing time of 80 ms (26). In all experiments the carrier frequency was set at the centre of the spectrum. The (^{1}H,^{13}C) HSQC (27) experiments were recorded with a delay of 3.5 ms (1*J* CH = 143 Hz) and the (^{1}H,^{13}C) HSQC-TOCSY experiment with a mixing time for proton–proton transfer of 80 ms to identify the network of one-bond and several proton–carbon connectivities, respectively. All data were processed with the XWINNMR software and one zero filling and π/3 phase shifted sine bell window function were applied in both dimensions before Fourier transform.

All NMR high resolution 1D and 2D detailed experiments data could also be transmitted to the interested persons from the corresponding author (CKJ, U de Moncton, Canada).

Mass spectroscopy

Mass spectra of all products were recorded on Agilent 6890 with mass selective detector (model 5973) (U de Moncton, Moncton, New Brunswick), the column used was a HP5-MS (30 m, 0.25 μm), the GC-MS EI and CI (NH_3) experiments on Riber 1030 GC-MS (U de Paris, Paris, France), and ESI-PI on a Micromass Quatro II (U de Paris, Paris, France), as well on an Agilent 19091S-436 with packed column HP5-MS (0.25 mm, 60 m, 0.25 μm) (Environment Canada, Ottawa, Canada). The GC-MS was used as the control of the progress of purification of chromatographic fractions for adduct **9b** and for the dichloro derivative **13c**. The mass spectroscopy was also used to determine the deuteration level of this last compound in a series of experiments as described in the following.

Molecular modelling

All molecular modelling results performed on HyperChem 6.02 on dienes and adducts are available on request from the corresponding author (CKJ, U de Moncton, Canada).

Microwaves

Microwave experiments were carried out at atmospheric pressure using a focused microwave reactor (CEM Discover™) (28) or MAP technology (14, 15). The instrument consists of a continuous focused microwave power output from 0 to 300W. Reactions were performed in a glass vessel equipped with a condenser; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 torr, tubes of 10 mL, sealed with a septum) (1 torr = 133.322 4 Pa). The temperature content of a vessel is monitored using a calibrated IR sensor mounted under the vessel. All experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a power of 300 W was selected and the reflux temperature was reached with a ramp of about 1 min. The time of the reaction does not include the ramp period.

Synthesis

*(4,10a-dimethyl-7b-*iso*-propyl-decaline-5ene)1a,4a-maleic acid anhydride (9b)*

Diels–Alder condensation of **1** with maleic anhydride (thermal reaction). Cubebene (**1**) (100 mg, ca. 0.5 mmol) and maleic anhydride (40 mg, 0.45 mmol, less than equimolar ratio) were dissolved in anhydrous toluene and heated in the stainless vessel for 24 h at 130 °C. Two consecutive flash column chromatography separations on silica gel column of adduct **9b** were then performed on the oily residue under TLC (hexane/ether 9:1, $R_f = 0.7$) and GC-MS controls (using mass chromatogram at m/z 302). The yield of pure adduct **9b** was 12% (16–18 mg) with an optical rotation of $\alpha_{25} = +38°$ (ethanol). MS eight main ions in **9b**, EI-spectrum m/z (I%): 302 (12, M^+), 274 (72), 259 (16), 231 (56), 203 (100), 185 (17), 164 (82), 145 (39).

Diels–Alder condensation of **1** with maleic anhydride (microwave reaction). Yield of **9b** 15%–23%. Conditions: CEM Discover™ 300 W at the reflux temperature of toluene for 5–30 min.

*4β,10β-dichloro-4α,10α-dimethyl-7β-*iso*-propyl-*trans-*decalin (13c)*

Addition of HCl to **1** at 0–5 °C. To a solution of α-cubebene (**1**) (90 mg, 0.5 mmol) in methanol (20 mL) (the equal volume of dry methanol saturated with hydrochloric acid (g) was added). The reaction mixture was left at 0–5 °C for 24 h then cautiously evaporated in vacuo. The resulting product **13c** (14 mg), mp 104–107 °C, TLC: petroleum ether, $R_f = 0.4$, isolated by column then by preparative TLC chromatographies on silica gel, yield 25%. In this separation, 31 mg of starting compound **1** and three unidentified compounds were separated. MS: For the compound **13c** CI-MS (NH_3) mass spectra revealed the presence of m/z 294 (100, NH_4^+), 277 (3, MH^+) 276 (2). The ESI spectrum confirmed double chlorination at m/z 277 (55, MH^+) and 279 (35, MH^+).

Addition of DCl to **1** was performed in a similar mode (also see ref. 3).

Synthesis by microwave-assisted addition of HCl

A solution of α-cubebene (100 mg, 0.5 mmol) in methanol (12.5 mL) (saturated with hydrochloric acid) was irradiated at 25 W with a ramp period of 1 min until reflux was reached. Heating of the solution was then maintained for 30 min, and after cooling the solvent was removed in vacuo. The various products observed by TLC analysis were then separated by column chromatography (petroleum ether) and analyzed as in previous procedure. Yield of **13c** 15%.

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