Improved synthesis of the chrysomelid pheromone (6*R*,7*S*)-(+)-himachala-9,11-diene via spontaneous bromination and didehydrobromination of 2,6,6,9-tetramethyl-bicyclo[5.4.0]undec-8-ene

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Dedicated to Professor Rainer Beckert on the occasion of his 60th birthday

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Abstract

A convenient synthesis of (6*R*,7*S*)-(+)-himachala-9,11-diene, the pheromone of the chrysomelid beetle *Phyllotreta striolata* is described. The diene is obtained in a single operation by a spontaneous "bromination/dehydrobromination" of 2,6,6,9-tetramethylbicyclo[5.4.0]undec-8-ene. The halogenation/dehalogenation sequence proceeds spontaneously in CCl_4, and is less uniform in CH_2Cl_2 and $CHCl_3$. ^{1}H NMR experiments carried out in presence of the radical scavenger di-*tert*-butyl-4-methylphenol suggest an ionic mechanism for this reaction. Theoretical calculations demonstrate that the spontaneous reaction profits from the strongly exergonic addition of Br_2 to the double bond and an almost neutral energy difference between the starting olefin and the diene pheromone.

Keywords: Spontaneous bromination/didehydrobromination, conjugated dienes, chrysomelid pheromone, *Phyllotreta striolata*

Introduction

Phyllotreta striolata is a pest with important economic consequences in Brassica crops, it is widely distributed in North America, Europe, and Asia.[1] This flea beetle belongs to the genus *Phyllotreta* (Coleoptera: Chrysomelidae) and is a specialized herbivore feeding on Brassicaceae and related plant families one and is of the most destructive beetle pests worldwide. In Southeast Asia, it is the dominant *Phyllotreta* species with up to eleven generations per year.[2] The adults feed mainly on host plant leaves, and females oviposit at the plant–soil interface. The larvae feed on root hairs of the host plants, and pupate in the soil.[3] Males of this species produce an aggregation pheromone that has been identified as (6*R*,7*S*)- (+)-himachala-9,11-diene (**5**). The structure was confirmed by rather lengthy synthetic approaches. Bartelt et. al. prepared **5** in nine steps and 6% of overall yield,[4] and Muto et. al. synthesized **5** in twelve steps (ca. 1% overall yield).[5] Recently we published a more efficient route starting from the natural sesquiterpene (–)-α-himachalene (**1**), that is readily available from the essential oil of *Cedrus atlantica*.[6]

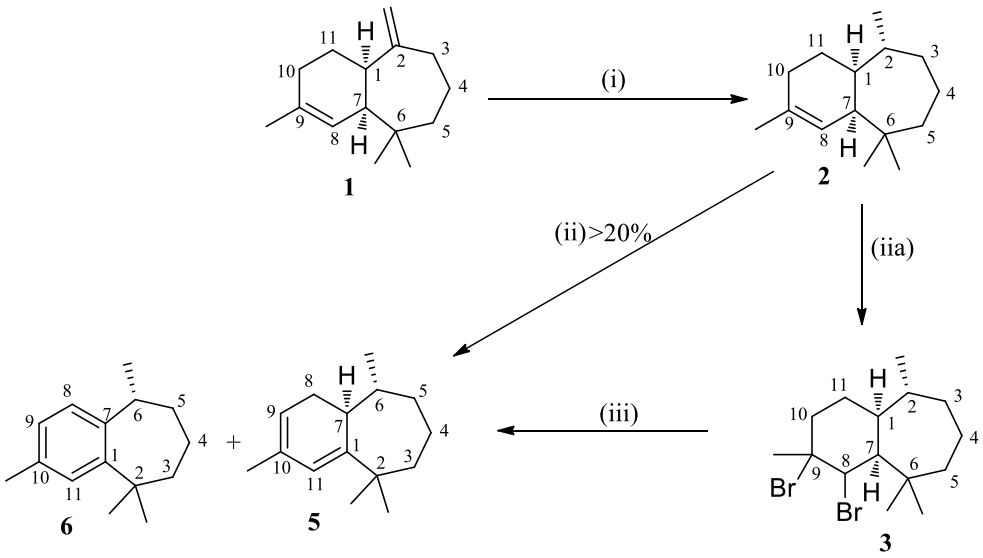
Although the improved synthesis required only three steps (Scheme 1, i-iia-iii), the access to the pheromone remained unsatisfactory, since **5** was only a minor component (4%) in a complex mixture that needed extensive purification by preparative GC.[6] Since field studies and behavioral assays require larger quantities of the bioactive compound, we were disposed to improve the sequence. While the initial hydrogenation of the exocyclic double bond of (-)-α-himachalene proceeded quantitatively,[6] the spontaneous one-pot bromination dehydrobromination sequence appeared to be a critical transformation yielding several products, among which an aromatic analogue (**6**) of the pheromone dominated after prolonged reaction times (48 h). Here we report a detailed analytical and quantum chemical approach to characterize the bromination/dehydrobromination sequence of 2,6,6,9-tetramethylbicyclo[5.4.0]undec-8-ene (**2**). Best synthetic results were obtained in an inert and nonpolar solvent such as CCl_4.

Results and Discussion

The pheromone was prepared *via* an optimized procedure requiring only two steps starting from (–)-α-himachalene **1** (Scheme 1) easily obtained by fractionated distillation of the essential oil of *Cedrus atlantica*. Catalytic hydrogenation of the exocyclic double bond of **1** was easily achieved with PtO_2/H_2 and afforded (1*S*,2*R*)-(**2**) as the major diastereomer (ca. 70-90%).[6]

Careful analysis of the bromination of **2** revealed different product profiles depending on the solvent employed. The yield of the expected *trans*-dibromide 1,2-dibromo-2,5,9,9-tetra-methyldecahydro-1H-benzo[7]annulene (**3**) was low in CCl_4 ($\varepsilon = 2.23$) and $CHCl_3$ ($\varepsilon = 4.81$), but higher in the more polar CH_2Cl_2 ($\varepsilon = 8.93$). In addition, monobrominated products along with the desired pheromone and aromatic products were formed (Table 1). The compound composition was estimated by GC-MS (uncorrected peak areas). Interestingly, in CCl_4 the whole sequence of bromination/dehydrobromination proceeded instantaneously and directly afforded the pheromone **5** in moderate yield (21%) along with allylic monobromides and the aromatic hydrocarbon **6**. Addition of bases, e.g. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,5-Diaza-

bicyclo[4.3.0]non-5-ene (DBN), was not required to generate the diene **5**. If the dibromide **3**, obtained independently from **2** by treatment with $CuBr_2/LiBr$[7] in THF/CH_3CN (35-55% yield) was stirred with DBU, only very low yields of **5** were obtained. Thus, the direct bromination/-dehydrobromination without addition of bases (DBU, DBN) proved to be the most efficient synthetic route to **5.** The improved procedure afforded the pheromone in a single operation and 16% yield after column chromatography on silica gel impregnated with $AgNO_3$ (20%). The eluting product was sufficiently pure (>91%) to perform field studies and behavioral assays.



Scheme 1. Synthesis of (6*R*,7*S*)-(+)himachala-9,11-diene. (i) Hydrogenation (PtO_2, H_2, in ethanol, RT. Only the (1*S*,2*R*)-isomer is shown. (ii) Br_2 in CCl_4, 0–5 °C (20%). (iia) Br_2 in $CHCl_3$, 0–5 °C. (iii) DBU, THF, RT (4%); Only the pheromone (6*R*,7*S*)-**5** is shown. IUPAC numbering was used.

Table 1. Major products of the spontaneous bromination/dehydrobromination of **2** in different solvents

Molecular formula	*m/z* (Da)	yield[i] (%)		
		CCl_4	$CHCl_3$	CH_2Cl_2
$C_{15}H_{24}$	**(5)** 204.3	21	5	8
$C_{15}H_{24}$	204.2[ii]	9	0.5	2
$C_{15}H_{23}Br$	282/284[iii]	25	2	38
$C_{15}H_{21}Br$	280/282[iii]	4	30	5
$C_{15}H_{26}Br_2$	**(3)** 362.0[iv]	7	3	18
$C_{15}H_{26}$	206.2[iii]	8	56	2
$C_{15}H_{22}$	**(6)** 202.2	4	11	8

(i) according to GC-MS (uncorrected peak areas). (ii) Isomer of **5**. **(**iii) Compound not isolated. (iv) Mixture of isomers of the dibromide **3**.

The spontaneous bromination/dehydrobromination reaction of **2** was also analyzed by ^{1}H NMR in CCl_4**.** Analysis of the olefinic region of the ^{1}H NMR spectra revealed an almost instantaneous loss of the signal for the single olefinic proton of **2** (δ = 5.37 ppm), accompanied by new signals for olefinic (δ = 5.40 – 5.65 ppm) and aromatic protons (δ = 6.70 – 7.05 ppm). Long reaction times (Figure 1 c,d) favored the formation of the thermodynamically more stable aromatic hydrocarbon **6**.

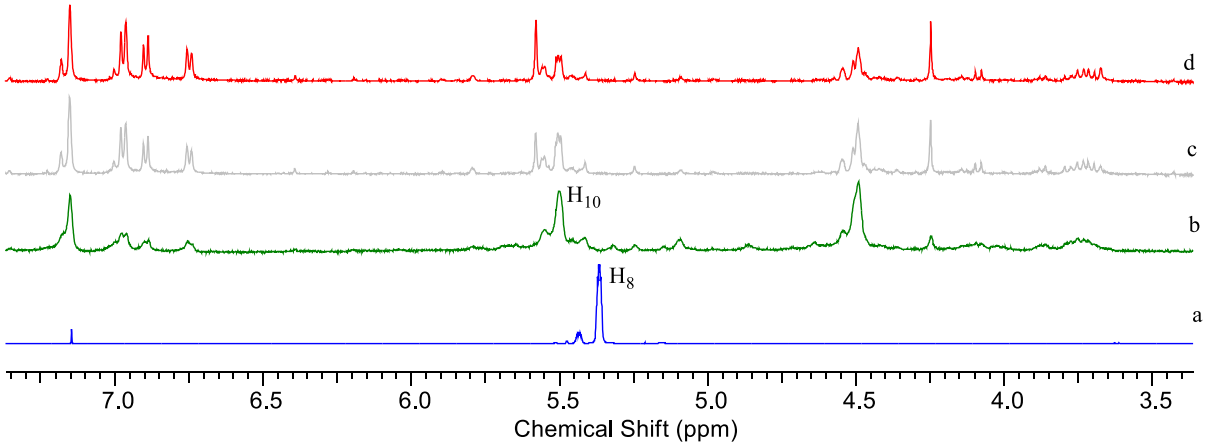


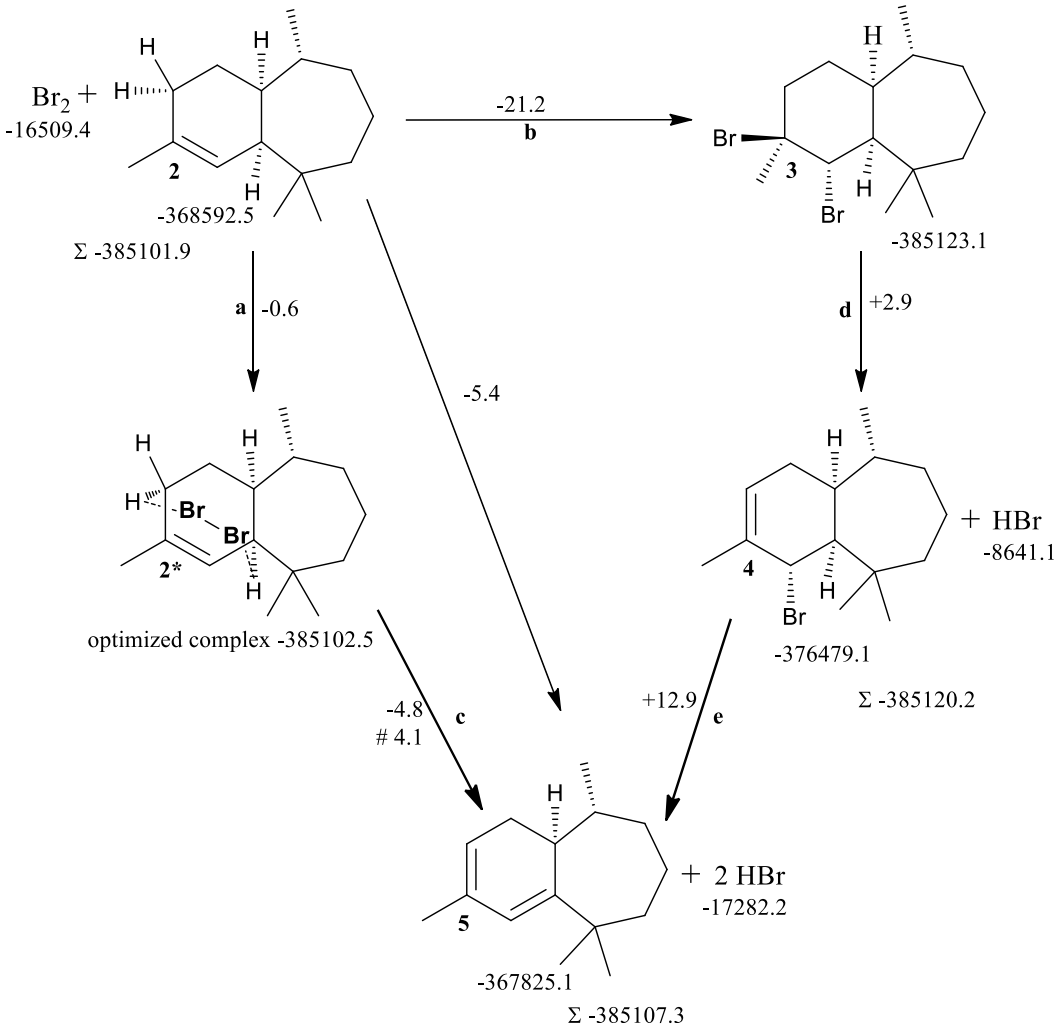
Figure 1. ^{1}H NMR spectrum of **2** (a); ^{1}H NMR spectra taken from the spontaneous bromination/-dehydrobromination of **2** in CCl_4 at different intervals (b-2min., c-24 hrs., d-48hrs.).

In line with product distribution of Table 1 and the NMR data, also quantum mechanical calculations supported a spontaneous bromination/dehydrobromination sequence. Two alternative mechanisms for the formation of the diene **5** were investigated by DFT-B3LYP calculations.

The first one started from **2** with addition of Br_2 (Scheme 2 b) to the double bond followed by elimination of two HBr molecules to yield the diene **5**. An alternative route calculated the homolytic cleavage of the Br_2 molecule by synchronous immediate attack onto both adjacent allylic hydrogen atoms at C7 and C10 resulting in **5** and two HBr molecules (Scheme 2 a-c). Although all calculations were carried out with spin-unrestricted DFT in none of the intermediate steps an isolated stable radical could be observed due to synchronous mechanisms in both alternative path ways.

In fact, the NMR data supported a rapid addition of Br_2 to the double bond of **2** followed by a stepwise elimination of HBr from **3**. Already after 2 minutes the first olefinic resonances of **5** or allylic monobromides appeared in the spectrum. Moreover, addition of a radical scavenger such as 2,6-di-*tert*-butyl-4-methylphenol BHT did not affect the reaction.[8] In line with these observations the calculated energies clearly support the addition of bromine across the double bond (-21.2 kcal/mol) as the first step. The bromide **3** looses HBr in a stepwise manner (Scheme

2, d-e). The first elimination of HBr generates the intermediate **4** and proceeds readily (+2.9 kcal/mol), while the elimination of the second HBr molecule is much more energetically disfavored (+12.9 kcal/mol). Overall, the spontaneous bromination/dehydrobromination sequence profits from the exergonic addition of Br_2 to the double bond along with the almost neutral energy difference between **2** and **5**. Compound **4** is supported by the NMR data since the signal of the olefinic proton H_{10} is already observed at a very early stage of the reaction (Figure 1 b). This signal disappears when the second molecule of HBr is eliminated which requires longer reaction times. Interestingly, the calculated energies of the compounds and corresponding reaction energies also favor the direct elimination (Scheme 2, steps a – c) since the reaction energies are negative for both steps. Three independent calculations have been performed for the Br_2 attack starting from the optimized complex **2***.



Scheme 2. Results of DFT-B3LYP calculations for two alternative reaction courses of the bromination/dehydrobromination of **2**. Values are given in kcal/mol. Energies listed below the

compounds result from energy optimizations of these structures. Those attached to the arrows are reaction energies and labeled with activation energies (#) respectively.

Reactions coordinate calculations were made for lowering one distance between bromine and the hydrogen atom to be abstracted in steps of 0.2 Å to 1.4 Å which would correspond to a stepwise reaction mechanism. However, in two cases no reaction could be observed and the energy continuously increased. In the third route both distances were lowered synchronously which leads to the formation of the product **5** with the corresponding loss of HBr (Figure 2). Although the calculated transition state geometry indicates not a 100% synchronous attack, the very low energy barrier of only 4.1 kcal/mol may favor this mechanism. Although this mechanism seems to be attractive according to the quantum mechanical calculations, the NMR analyses in the presence of the radical scavenger BHT, clearly demonstrate that the formation of the diene **5** proceeds via the dibromide **3** and/or allylic bromide intermediates; free radicals are apparently not involved in the reaction.

Conclusions

The chrysomelid pheromone **5** can be easily and in good yield prepared from **1** by a spontaneous bromination/didehydrobromination approach using CCl_4 as solvent. Purification is easily achieved by chromatography on silica gel impregnated with $AgNO_3$ (20%). Quantum mechanical calculations and NMR studies support an ionic addition of Br_2 to the alkene **2**, followed by elimination of HBr.

Experimental Section

General. NMR spectra were recorded at 300K on a Bruker DRX500 spectrometer. ^{1}H NMR: Chemical shifts are referenced relative to the residual proton signal of C_6D_6. Reactions were followed by Gas Chromatography-Mass Spectrometry (GC-MS), using a ThermoQuest CE Instruments GC 2000 Series coupled to a ThermoQuest Finnigan Trace MS mass spectrometer.[6] Separation was achieved on a HP-5MS capillary column (15 m × 0,25 mm ID with 0,25 µm film thickness, Phenomenex) under programmed conditions: 50 °C (3 min) at 15 °C min^{-1} to 180 °C (4 min) and at 10 °C min^{-1} to 260 °C (5 min). Injection port: 250 °C. Helium at 1.5 ml min^{-1} served as carrier gas. Solvents were purified prior to use by conventional methods. Bromine was dried over equal volume of concentrated sulfuric acid. The starting compound **1** was distilled from *Cedrus atlantica* essential oil under reduced pressure (2.5 mbar) through a 170 cm column filled with Sulzer DX packing (Sulzer Chemtech AG, Switzerland), and was obtained with a purity of 97.5%. The relative stereochemistry was ascertained by NMR.[9]

(6*R*,7*S*)-(+)-Himachala-9,11-diene (5). The pheromone **5** was obtained in good yield by treatment of **2** with bromine in carbontetrachloride (CCl_4). The olefin **2** (5,66 g, 27,4 mmol) was dissolved in CCl_4 (80 ml) and the solution was cooled to 0–5 °C in ice bath. Argon was passed through a solution of bromine (4,63 g, 29 mmol) in CCl_4 (40 ml) and the argon stream, loaded with Br_2 was passed into the solution of the alkene over a period of 120 min. Stirring was continued at room temperature for another 30 min until the color of the Br_2 disappeared while keeping a gentle argon flow. The solution was concentrated under vacuum, and the residue (6.33 g) was pre-purified by flash chromatography on SiO_2 using n-hexane for elution. The solvent was removed under vacuum in the presence of ca. 2.0 g of silica, and the remaining solid with the absorbed products were loaded onto a column with 120 g of SiO_2 impregnated with $AgNO_3$ (20%). The diene **5** was eluted with pentane. Yield: 894 mg (16%) of the pure pheromone (> 91% according to GC-MS). The spectroscopic data of **5** were in agreement with literature data.[5,6] Compound **5** was also prepared in chloroform and dichloromethane following the procedure described above.

^{1}H NMR. 25 mg of **2** were dissolved in a mixture of 500/100 µL CCl_4/C_6D_6 and a small excess of Br_2 was added. ^{1}H NMR spectra were taken at different intervals (2 min, 24 h and 48 h). For experiments in the presence of BHT, c.a. 5% of the radical scavenger was added before bromine.

Quantum mechanical calculations for mechanistic studies

Calculations were carried out with JAGUAR[10] using spin-unrestricted DFT B3LYP with the LACV3P**++ basis set which includes an effective core potential. All starting structures were first optimized with accurate level. Subsequently relaxed coordinate scans were performed for several alternative reaction mechanisms to be studied by changing distances between atoms under consideration for reactions to be investigated in steps of 0.2 Å to the desired distance. Based on these calculations the QST option was applied to determine the transition states of the reactions. For this purpose three structures have to be submitted for the calculations, the optimized starting structure, the detected approximate transition state structure from the reaction-coordinate scan and the products structure.

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