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Kinetic Resolution in Transannular Morita-Baylis-Hillman Reaction: An Approximation to the Synthesis of Sesquiterpenes from Guaiane Family

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Abstract: An approximation to the synthesis of several sesquiterpenes from the Guaiane family is described in which the core structure was obtained through a transannular Morita-Baylis-Hillman reaction performed under kinetic resolution. Several manipulations of the obtained MBH adduct have been carried out directed towards the total synthesis of γ-Gurjunene, to the formal synthesis of Clavukerin A, to the synthesis of a non-natural isomer of *isoguaiane* and to the synthesis of an advanced intermediate in the total synthesis of Palustrol.

Keywords: Morita-Baylis-Hillman; transannular; kinetic resolution; sesquiterpene; phosphine; catalysis; natural product; Palustrol; Clavukerin A; guaiene

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1. Introduction

Polycyclic structures are common motifs present in the structural core of many natural products [1]. The biological activity exhibited by some of these compounds, has inspired the development of many pharmaceutically active compounds and therefore it has attracted the attention of the synthetic community in order to develop new efficient approaches for their preparation [2]. In particular, the lack of supply or isolation difficulties of such polycyclic bioactive compounds, have brought to light the need for new strategies for the stereocontrolled construction of polycyclic scaffolds, in view of the key role played by the three-dimensional arrangement of these molecules with respect to the interaction with the corresponding biological receptor that accounts for the physiological response [3]. In this sense, synthetic chemists have contributed to this field not only by the development of synthetic routes to access biologically active compounds, but also by providing critical information regarding the structure-activity relationship [4]. In the field of natural products, the hydroazulene bicyclic system is a substructure commonly present as part of the structural core of different families of sesquiterpenoids, such as aromadendrane or guaiane families, both characterized by the presence of a cyclopropane unit or a lateral three carbon atom chain attached to the seven-membered ring moiety respectively (Figure 1) [5].

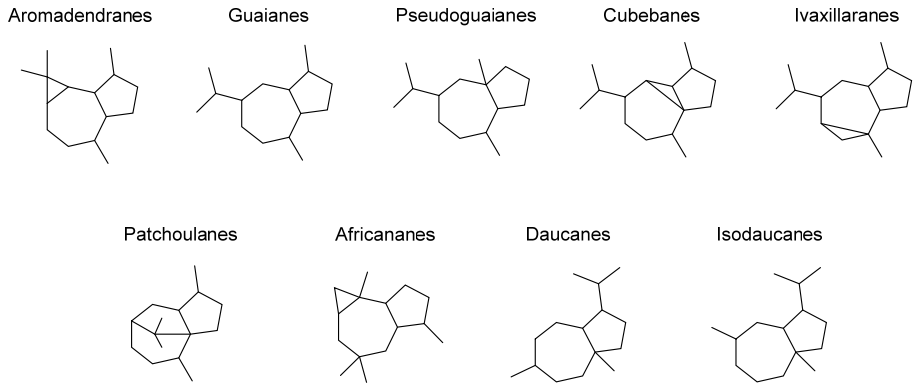
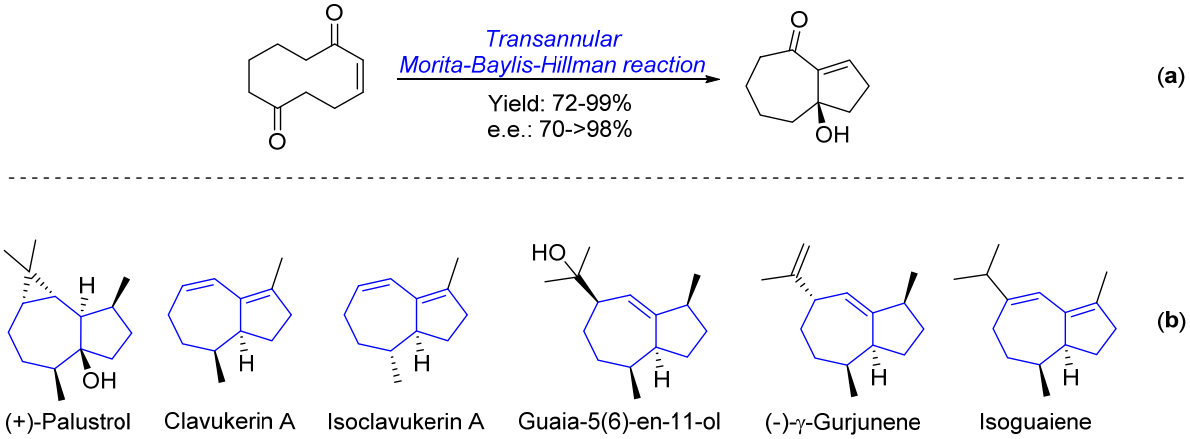


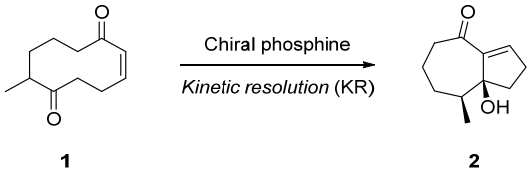
Figure 1. Sesquiterpenoid families containing hydroazulene core.

Although, most of these natural products have been commonly isolated from essential oils extracted from different plants and trees, in the last years marine organisms have arisen as a surprisingly prolific source of these biologically active sesquiterpenoids [6–10]. Despite this natural availability, some sesquiterpenoids still remain relatively inaccessible, pinpointing the necessity for the development of efficient synthetic routes. In this sense, the enantioselective transannular Morita-Baylis-Hillman reaction catalyzed by chiral bifunctional phosphines developed by us (Scheme 1a), [11] has demonstrated to be a suitable strategy to access the bicyclo[5.3.0]decane scaffold, a structural core found in different sesquiterpenoids such as Palustrol, Clavukerin A, γ gurjunene or guaia-5(6)-en-11-ol among others (Scheme 1b).



Scheme 1. (**a**) Enantioselective Morita-Baylis-Hillman reaction developed in our group; (**b**) Representative examples of sesquiterpenoids containing bicyclo[5.3.0]decane scaffold.

Although huge progresses have been made in this field towards the synthesis of some of these compounds, most of the reported approaches rely on the chiral pool methodology, being in some cases necessary the employment of related sesquiterpenoids as starting materials [12–27]. Considering that the mentioned catalytic enantioselective transannular Morita-Baylis-Hillman reaction developed in our group could be employed as key step in the total synthesis of some of these sesquiterpenoids, we wish to present herein different approaches to several of these compounds using this reaction as key step. In this regard, as all the synthetic targets contain a methyl group at C-8 position, we envisioned that a racemic substrate bearing a methyl group such as **1** could be employed as starting material. A kinetic resolution process (KR) for the generation of the enantiopure adduct **2** could be employed and being this the starting material of the abovementioned sesquiterpenoids (Scheme 2).

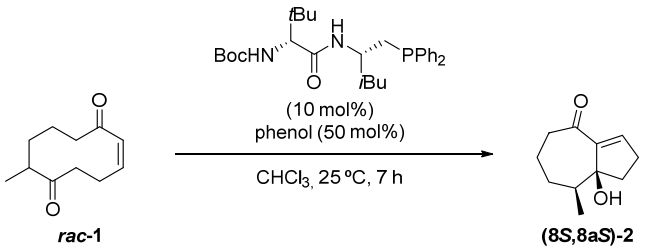


Scheme 2. Projected kinetic resolution through catalytic enantioselective Morita-Baylis-Hillman reaction.

2. Results and Discussion

2.1. Transannular Kinetic Resolution

We proceeded with the study of the key kinetic resolution step. In this sense, preliminary experiments were carried out by subjecting racemic substrate **1** to the previously optimized conditions for the transannular Morita-Baylis-Hillman process using a chiral phosphine as catalyst (Scheme 3). The reaction was monitored by TLC and, after 7 h, full conversion of the starting material was observed. Under these conditions, adduct **2** was isolated in excellent yield and as a 5:1 mixture of diastereomers, albeit low enantiomeric excess was obtained for the major diastereomer. However, when the analogous reaction was quenched after one hour, adduct **2** could be isolated in 50% yield as a mixture of diastereomers, determining 70% e.e. for the major diastereomer and 55% e.e. for the minor diastereomer.



t	conv.	Yield	d.r.	e.e. (major/minor)
7h	100%	99%	5:1	20%/85%
1h	55%	50%	2:1	70%/55%

Scheme 3. Preliminary results for the transannular Morita-Baylis-Hillman reaction.

In view of these preliminary results, we decided to carry out a set of reactions under the same experimental conditions, in order to evaluate the dependence of e.e. and d.r. with conversion. However, NMR analysis of crude reaction mixtures showed that the reaction was continuing after work-up due to the presence of all reactive species together with the catalyst in the crude mixture. For this reason, an appropriate method was necessary in order to quench the reaction at the desired time. This method should deactivate the catalyst without affecting either the product of the reaction or the unreacted starting material. In this sense, a work-up in which the phosphine is oxidized to the corresponding phosphine oxide emerged as a suitable strategy. Based on literature precedents [28–32], different oxidizing reagents were surveyed such as peracetic acid, *m*-chloroperbenzoic acid (MCPBA) and hydrogen peroxide. Catalyst oxidation could be easily followed by ^{31}P-NMR, due to the significant shift of the NMR signal that takes place, being around −25 ppm for active catalyst whilst shifts to +30 ppm for corresponding phosphine oxide. After a survey, hydrogen peroxide was chosen as the best option as it provided immediate full deactivation of the catalyst with no side product formation.

Once we found an appropriate experimental procedure for this purpose, we applied the previously optimized conditions for the enantioselective transannular process to a series of identical reactions (Table 1). However, despite different reaction times were evaluated (entries 1–4), none of them provided satisfactory results, achieving a 39% yield of the desired product, with a d.r. of 15:1 and 88% e.e. for the major diastereoisomers as best results when the reaction was quenched after 50 min (entry 3). Alternatively, when the solvent

was changed from chloroform to carbon tetrachloride, a significant increase in reaction rate was observed, which allowed us to lower the temperature to 5 °C (entry 5). Under these conditions, after 20 min adduct **2** was isolated in 46% yield as a single diastereomer (>20:1) and with excellent enantioselectivity. At this point, it was decided to scale up the reaction to 0.8 mmol of **1** before facing a more comprehensive evaluation of the reaction time parameter (entry 6). Following this methodology, we were able to determine that the reaction should be quenched after 30 min to access adduct **(8*S*,8a*S*)-2** as a single diastereomer (>20:1) in good yield (42%) and high enantiomeric excess (90%). Further recrystallization in hexane increased the enantiopurity of adduct **(8*S*,8a*S*)-2** up to a 98% e.e.

Table 1. Preliminary kinetic resolution studies [1].

Entry	Solvent	T (°C)	Time (min)	Recovered 1 (%)	e.e. 1 (%) [2]	Yield 2 (%)	e.e. 2 (%) [2]
1	$CHCl_3$	25	40	61	50	35	88
2	$CHCl_3$	25	45	62	54	37	88
3	$CHCl_3$	25	50	57	54	39	88
4	$CHCl_3$	25	55	50	66	42	86
5	CCl_4	5	20	-	-	46	90
6 [3]	CCl_4	5	30	56	76	42	90

[1] Reactions performed at 0.1 mmol scale employing 10 mol% of catalyst and 50 mol% of phenol in $CHCl_3$ (0.1 mmol/mL) at room temperature. Diastereomeric ratio for product **2** was >15:1 in all the cases. Yields refer to isolated pure products. [2] Calculated by HPLC on chiral stationary phase. [3] Reactions performed at 0.8 mmol scale.

The absolute configuration of adduct **(8*S*,8a*S*)-2** and of the resolved unreacted starting material **(*R*)-1** could be determined by single crystal X-ray diffraction (Figure 2) [11].

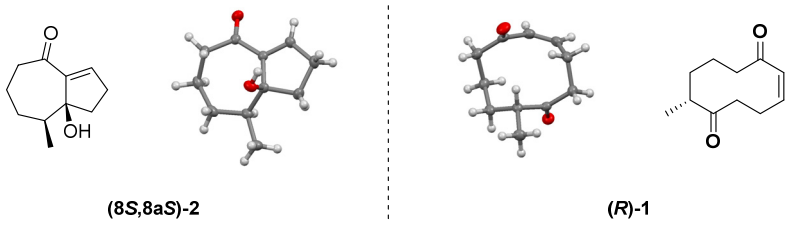
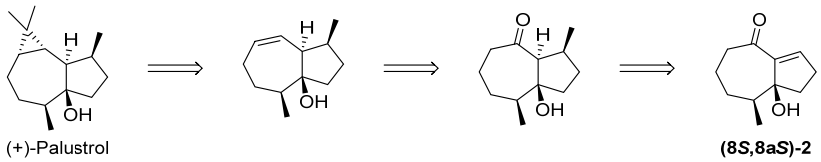


Figure 2. Stereostructures for bicyclic **(8*S*,8a*S*)-2** and unreacted starting material **(*R*)-1**.

2.2. Preparation of an Advanced Intermediate in the Synthesis of Palustrol

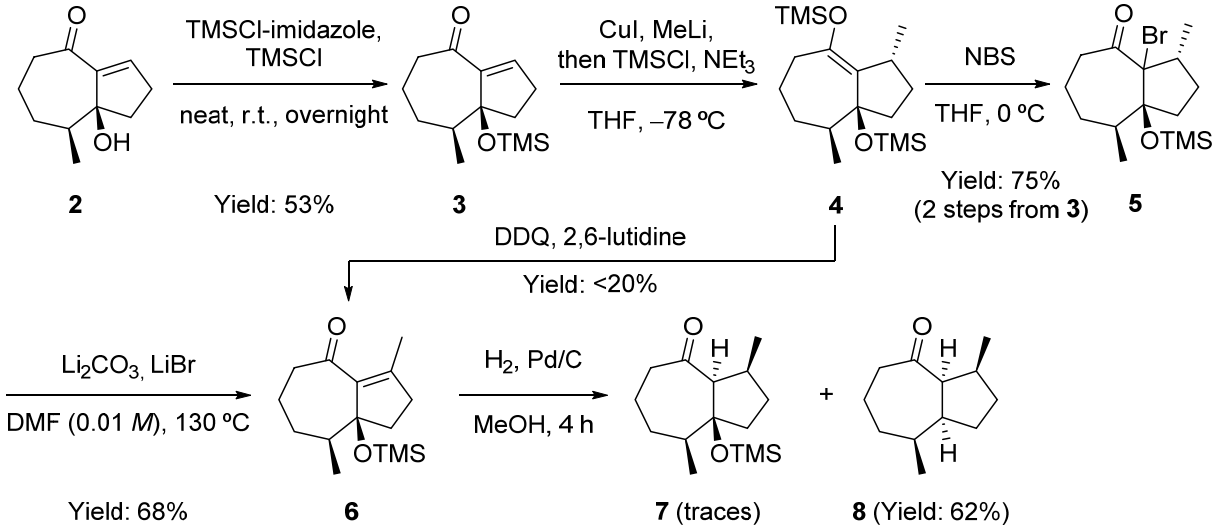
Once we found efficient experimental conditions for the synthesis of adduct **(8*S*,8a*S*)-2**, we continued with the planned strategy for the synthesis of (+)-Palustrol. As shown in Scheme 4, the cyclopropane moiety was proposed to be constructed by cyclopropanation of an alkene, which could be as well generated by reduction of the corresponding ketone and subsequent elimination. The methyl group at C-4 was proposed to arise from a conjugate addition across the Morita-Baylis-Hillman bicyclic adduct.



Scheme 4. Retrosynthetic analysis for the synthesis of (+)-Palustrol starting from **(8*S*,8a*S*)-2**.

First of all [11], the protection of the alcohol moiety had to be carried out in order to prevent any interference of this functional group in the subsequent chemical transformations. Unfortunately, this protection resulted as much more challenging than expected, due to either the steric hindrance and/or the allylic nature of this alcohol. Substrate **2**

remained unreactive under several protection conditions tested, such as acetylation, benzylation or methoxymethyl acetal formation. Additionally, common procedures for the introduction of silyl protecting groups using the corresponding silyl chlorides did not afford the protected product [33,34], while more reactive reagents such as silyl triflates or higher temperatures produced decomposition of the starting material. Fortunately, when TMS Imidazole was employed as trimethylsilyl source [35], product **3** could be isolated in 53% yield (Scheme 5). Analogous procedures for bulkier silyl protecting groups did not provide the corresponding protected products. Next, we proceeded with the projected conjugate addition of Me_2CuLi to the α,β unsaturated system. Unfortunately, after the conjugate addition reaction, the resulting product turned out to be extremely unstable, being necessary to trap the enolate intermediate as the corresponding silyl enol ether. In this way, the preformed Gilman reagent was added at −78 °C over adduct **3**, followed by the addition of TMSCl and NEt_3 [36–38]. The resulting silyl enol ether was isolated and subjected to DDQ-mediated oxidation to produce compound **6** in very low yields. On the other hand, in situ bromination of silyl enol ether intermediate **4** afforded compound **5** as a single diastereomer in 75% yield over two steps [39]. Next, base-promoted elimination using a literature procedure (Li_2CO_3, LiBr in DMF at high temperature) converted **5** into **6** in good overall yield [40–42]. This elimination step turned out to be quite sensitive to concentration, resulting in complex product mixtures when concentrated conditions were employed. Fortunately, high diluted conditions (0.01 M) as applied by Baran et al. [43] significantly improved the performance of the reaction affording product **6** in 68% yield. It should be mentioned that it was required to increase the temperature to 130 °C to promote the reaction, compared to the 60 °C used in the literature procedure.



Scheme 5. Synthesis of compound **8** [11].

At this point, adduct **6** was subjected to standard hydrogenation conditions (H_2, Pd/C, MeOH) in order to afford product **7**. However, in spite of the expected hydrogenated product, compound **8** was obtained, in which trimethylsilyloxy group had been lost. The formation of this product was attributed to the reduction of the C-C double bond, as well as concomitant cleavage of silyl protecting group [44] and subsequent spontaneous elimination of the alcohol and second hydrogenation of the resulting product. In any case, after 4 h of reaction time, full consumption of the starting material was observed by TLC, allowing the isolation of adduct **8** in 62% yield by flash column chromatography.

The relative configuration of the stereocenters in the molecule could be determined by X-ray diffraction of the corresponding hydrazone **9** (Figure 3). It should be mentioned that the absolute configuration at C-3a in compound **(3*S**,3a*S**,8*S**,8a*S**)-8** is thought to be opposite to that determined for hydrazone **(3*S**,3a*R**,8*S**,8a*S**)-9** (CCDC 2118404), taking

into account that catalytic hydrogenation is expected to take place through *syn* addition. Epimerization at α position to carbonyl is believed to occur under hydrazone formation conditions ($TsNHNH_2$, EtOH, HOAc, H_2SO_4 cat., r.t.).

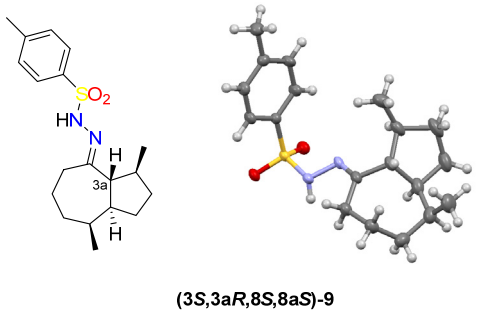
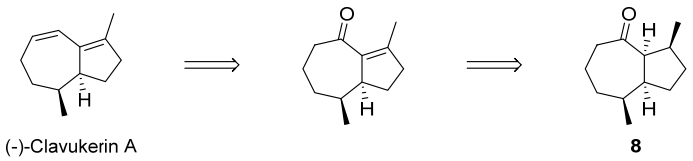


Figure 3. Stereostructure for bicyclic **(3*S**,3a*R**,8*S**,8a*S**)-9**.

At this point, and in order to overcome the undesired deoxygenation, different reported methodologies for conjugate reduction using hydrides were tested. Adduct **6** remained unreactive when exposed to stoichiometric amounts of $[(Ph_3P)CuH]_6$, commonly known as Stryker reagent [45,46]. Modification of classical conditions (benzene, r.t.) by increasing the temperature led to complex mixtures of products or complete decomposition of the starting material without observing, in any case, detectable amounts of the desired product. The use of other reported efficient catalytic systems for the conjugate reduction of enones, such as $Et_3SiH/[RhCl(PPh_3)_3]$ or PhMeSiH/CuCl, [47,48] did not afford the desired product. After several attempts, the discouraging results obtained led us to discard the present synthetic strategy.

2.3. Formal Total Synthesis of Clavukerin A

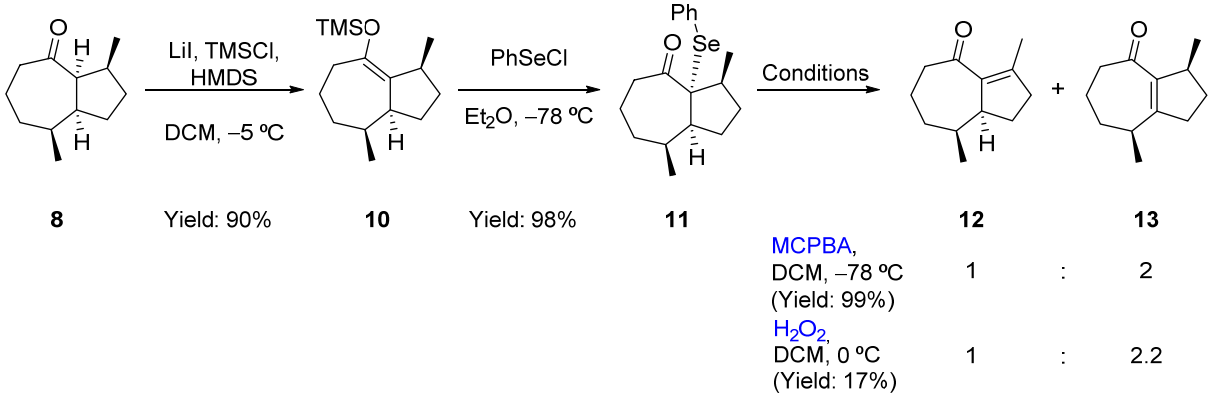
As hydrogenation of compound **6** led to the loss of the alcohol moiety present in the molecule, which prevented us from accessing (+)-Palustrol, we decided to accomplish the synthesis of (−)-Clavukerin A, as it should be accessed from adduct **8**. As shown in Scheme 6 a carbonyl reduction/elimination was proposed for the final construction of the diene system, from a bicyclic α,β-unsaturated ketone, which could be accessed from the aforementioned compound **8**.



Scheme 6. Retrosynthetic analysis for the synthesis of (−)-Clavukerin A starting from **8**.

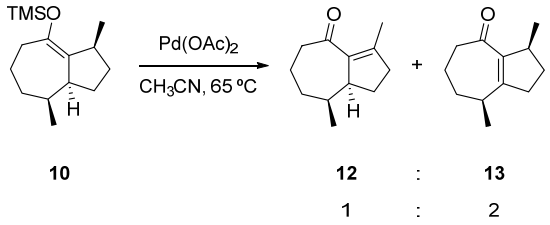
Our initial attempts were directed to restore the α,β-unsaturated system in the molecule leading to an enone intermediate, whose transformation into (−)-Clavukerin A has already been described in the literature. In order to achieve this objective, we considered several strategies. First of all, compound **8** was transformed into the corresponding silyl enol ether **10** [49,50] and directly exposed to phenylselenyl chloride in Et_2O at −78 °C, affording selenide **11** as a single diastereomer, presumably due to the formation of the new C-Se bond through the less hindered face of the silyl enol ether (Scheme 7). Next, adduct **11** was subjected to standard conditions for the oxidation to selenoxide and in situ elimination [51,52]. Unfortunately, when MCPBA was employed as oxidant in dichloromethane at −78 °C, a 2:1 mixture of regioisomers was obtained and NMR analysis (see Supplementary Materials) allowed us to identify these products as regioisomeric α,β-unsaturated ketones **12** and **13**, being the undesired product **13** formed as the main product. The use of H_2O_2 as an alternative oxidant did not provide any improvement on the outcome of the

reaction, affording products **12** and **13** in a similar ratio. The observed lack of selectivity was attributed to the *cis* orientation of both hydrogens in the two β positions with respect to the selenide. As selenide-mediated eliminations are described to take place through a *syn* arrangement [53–55], this would imply that elimination could take place in both positions. Although it was expected that β hydrogen in the cyclopentane ring would be more accessible than the β hydrogen in the fused system, experimental observations showed a preferred formation of product **13**.



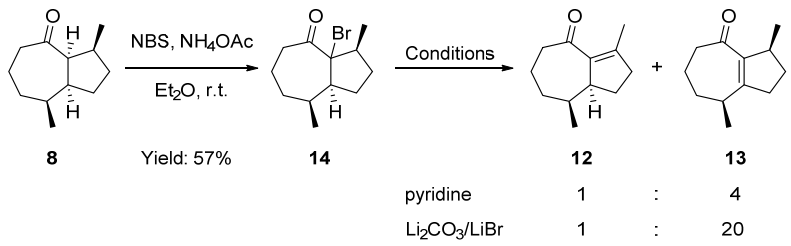
Scheme 7. Synthesis of compound **11** and elimination reaction to form enone **12**.

An alternative approach for the construction of the α,β-unsaturated system was also tested by subjecting silyl enol ether **10** to Ito-Saegusa conditions [56–59]. However, when adduct **8** was exposed to $Pd(OAc)_2$ in CH_3CN at 65 °C, a 2:1 mixture of regioisomers was obtained, being **12** and undesired enone **13** formed as main product (Scheme 8).



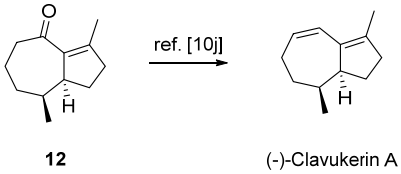
Scheme 8. Ito-Saegusa approach for the synthesis of enone **12**.

Other elimination procedures were also surveyed. In this sense, α-bromoketone intermediate **14** was synthesized by treatment of adduct **8** with *N*-bromosuccinimide in Et_2O at room temperature in presence of 10 mol% of NH_4OAc [60], and subsequently exposed to different bases (Scheme 9). While DBU, NaH and LiHMDS did not promote the elimination process, even at high temperatures; pyridine, as well as previously applied conditions involving Li_2CO_3/LiBr rendered products **12** and **13** in a 1:4 and 1:20 ratio, respectively.



Scheme 9. Elimination through bromoketone **14**.

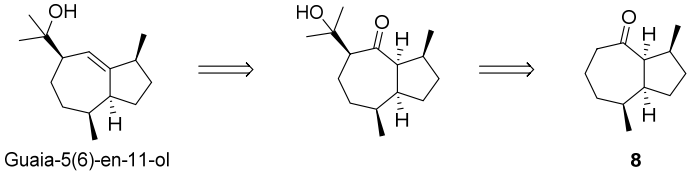
Although the different elimination protocols did not afford compound **12** as the major adduct, this methodology represents a formal total synthesis of (−)-Clavukerin A (Scheme 10) [43].



Scheme 10. Formal total synthesis of (−)-Clavukerin A.

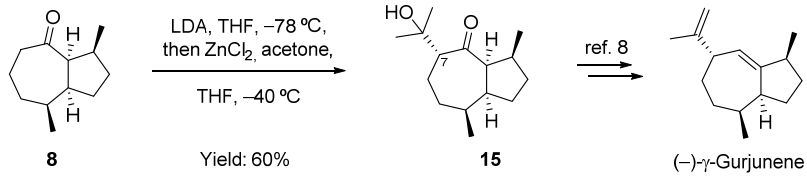
2.4. Attempt to the Synthesis Guaia-5(6)-en-11-ol; Synthesis of (−)-γ-Gurjunene and Non-Natural 1-epi-11,12-didehydro-4,5-dihydroisoguaiane

In view of the obtained results, we decided now to focus our efforts on the synthesis of Guaia-5(6)-en-11-ol, a sesquiterpenoid from the guaiane family with a very related structure and that was expected to be readily accessible from adduct **8** (Scheme 11).



Scheme 11. Retrosynthetic analysis for the synthesis of Guaia-5(6)-en-11-ol starting from **8**.

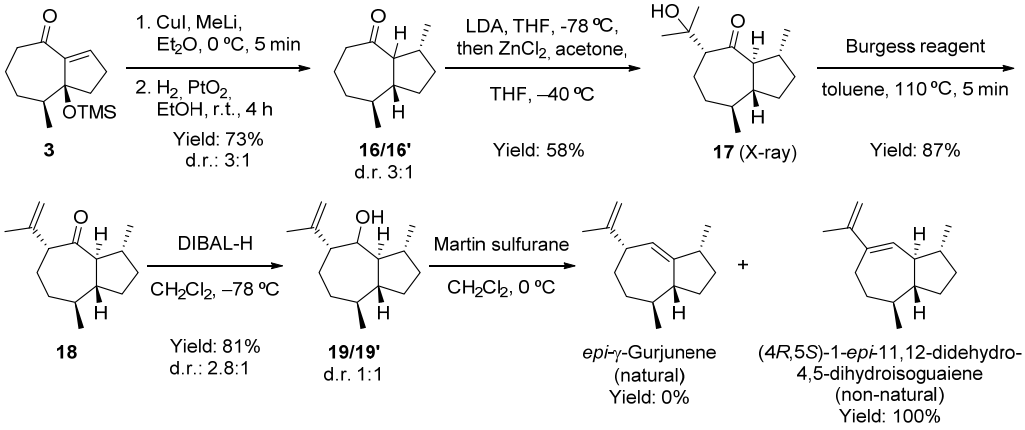
Taking this fact into account we initially introduced the lateral three atom carbon chain through aldol reaction. For this purpose, a kinetic deprotonation was performed with LDA at −78 °C followed by zinc chloride-promoted aldol reaction [61,62], affording adduct **15** as a single diastereomer in 60% yield, although with the wrong configuration at the newly generated stereogenic center (Scheme 12). The relative stereochemistry of the new stereocenter was determined by NMR analysis, through the observation of nuclear Overhauser effect (n.O.e.) between the hydrogen atom at C-7 and the methyl groups at C-4 and C-10. Therefore, it was concluded that aldol **15** could not be employed as precursor in the total synthesis of Guaia-5(6)-en-11-ol, although we could use it successfully for the total synthesis of (−)-γ-Gurjunene as reported earlier by us [11].



Scheme 12. Aldol reaction for the synthesis of **15** and application to the synthesis of (−)-γ-Gurjunene.

Nevertheless, we directed our attention to the possibility of synthesizing the natural isomer of this compound *epi*-γ-Gurjunene, which was conducted starting from compound **3** (Scheme 13). Thus, conjugate addition of Gilman cuprate was subsequently followed by in situ catalytic hydrogenation, delivering the corresponding adduct in 73% yield as a 3:1 mixture of epimers (**16** and **16′**) at the α-stereocentre to the ketone moiety, which is not relevant for the total synthesis as this stereocentre is not present on the final product. Next, aldol reaction was carried out under the same conditions as shown before, providing compound **16** (CCDC 2118405) as a single diastereoisomer and whose stereostructure could be confirmed by X-ray analysis. Compound **17** was next submitted to elimination reaction with Burgess reagent in order to obtain the isopropenyl alkyl chain in **18**. Finally, DIBAL-H promoted carbonyl reduction produced a mixture of isomers **19** and **19′** which were

subjected to a second elimination reaction using Martin sulfurane. However, all attempts to obtain *epi*-γ-Gurjunene were not successful leading in all cases to the isolation of 1-*epi*-11,12-didehydro-4,5-dihydroisoguaiene, which is the non-natural isomer of isoguaiene.



Scheme 13. Attempts to the synthesis of natural *epi*-γ-Gurjunene that led to the synthesis of *epi*-didehydrodihydroisoguaiene.

3. Materials and Methods

Nuclear magnetic resonance proton and carbon spectra (^{1}H NMR, ^{13}C NMR) were acquired at 25 °C on a Bruker AC-300 spectrometer (Bruker BioSpin GmbH, Silberstreifen 4, 76287 Rheinstetten, Billerica, MA, USA), infrared spectra (IR) in a Jasco FT/IR 4100 (ATR) (Jasco, Hachioji, Tokyo 193-0835, Japan) and high-resolution mass spectra (HRMS) on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2) using electrospray ionization (ESI^+) (Waters, Milford, MA, United States). X-ray data collections were performed in an Agilent Supernova diffractometer (Agilent, Santa Clara, CA, United States). Solvents and reagents were used without further purification. Anhydrous solvents were dried with activated molecular sieves [63,64]. Thermo Haake EK90 refrigerators (Thermo Fisher Scientific Inc., Waltham, MA, USA) were used for performing reactions at reduced temperatures. For flash chromatography Silicycle 40–63, 230–400 mesh silica gel was used (SiliCycle Inc., Quebec, QC, Canada) [65]. Removal of the solvents were performed under reduced pressure Büchi R-2 series rotatory evaporators (Buchi, Flawil, Switzerland). Precision weighing was made in a Sartorius Analytical Balance (± 0.1 mg) (Sartorius, Goettingen, Germany). Note: Except those reactions performed during the synthesis of (−)-γ-Gurjunene (Scheme 12) for which enantiomerically pure **(8*S*,8a*S*)-2** was used, the syntheses described herein were accomplished in a racemic manner. The authors reserve the right to carry out the reactions described herein enantioselectively. For further details see "Supplementary Materials":

N′-((3*S**,3a*R**,4*E*,8*S**,8a*S**)-3,8-dimethyloctahydroazulen-4(1*H*)-ylidene)-4-methylbenzenesulfonohydrazide (**9**). To a solution of compound **8** (15.5 mg, 0.086 mmol) in EtOH (1.3 mL) at rt, tosylhydrazine (20 mg, 0.107 mmol) and acetic acid (8 µL, 0.140 mmol) were subsequently added. The mixture was stirred at rt during 8 days. The crude product was evaporated and purified by flash column chromatography (petroleum ether/EtOAc 8:1) affording the desired compound **9** (2.99 mg, 0.0086 mmol) as a white solid that easily decompose in solution. Yield: 10%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.81 (m, 2H), 7.31–7.27 (m, 2H), 7.17–7.07 (bs, 1H), 2.42 (s, 3H), 2.38–2.23 (m, 2H), 2.15–2.02 (m, 2H), 2.01–1.85 (m, 2H), 1.75–1.65 (m, 4H), 1.64–1.48 (m, 2H), 1.45–1.32 (m, 2H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H). HRMS: Calculated for $[C_{19}H_{29}N_2O_2S]^+$: 349.1944 $[(M + H)^+]$; found: 349.1950. M.p. (petroleum ether/EtOAc): melted.

(((3*S**,8*S**,8a*S**)-3,8-dimethyl-1,2,3,5,6,7,8,8a-octahydroazulen-4-yl)oxy)trimethylsilane (**10**). To a solution of compound **8** (9.0 mg, 0.050 mmol) in dry CH_2Cl_2 (0.3 mL) at −5 °C (ice/NaCl bath) HMDS (13.5 µL, 0.0645 mmol) was added. The mixture was stirred for

1 min and then previously dried LiI (7.6 mg, 0.0565 mmol) and TMSCl (6.3 µL, 0.05 mmol) were subsequently added. The mixture was stirred at −5 °C for 160 min observing the appearance of a white suspension. The crude product was then poured into ice and CH_2Cl_2 (5 mL) and a saturated solution of $NaHCO_3$ (5 mL) was added. The phases were separated and the organic layer washed with a saturated solution of $NaHCO_3$ (5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent eliminated under reduced pressure affording the desired compound **10** (11.3 mg, 0.045 mmol) as a colorless oil that easily decomposes in solution. Yield: 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73 (dt, *J* = 23.9, 8.2 Hz, 2H), 2.41–2.27 (m, 1H), 2.07 (dd, *J* = 15.7, 6.6 Hz, 1H), 1.90–1.78 (m, 1H), 1.78–1.23 (m, 8H), 0.95 (d, *J* = 7.3 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.18 (s, 9H). HRMS: Calculated for $[C_{18}H_{29}OSi]^+$: 253.1982 [(M + H)$^+$]; found: 253.1986.

(3*S**,3a*R**,8*S**,8a*S**)-3,8-dimethyl-3a-(phenylselanyl)octahydroazulen-4(1*H*)-one (**11**). To a solution of the compound **10** (11.3 mg, 0.045 mmol) in dry Et_2O (0.14 mL) at −78 °C a solution of PhSeCl (9.0 mg, 0.047 mmol) in dry Et_2O (0.10 mL) was added. The mixture was stirred at −78 °C for 2 h. Then, a saturated solution of $NaHCO_3$ (5 mL) and Et_2O (5 mL) were added. The phases were separated, washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, filtered and the solvent eliminated under reduced pressure affording the desired compound **11** (15.1 mg, 0.044 mmol) as a colorless oil. Yield: 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.52 (m, 2H), 7.43–7.23 (m, 3H), 2.54 (ddd, *J* = 11.4, 7.2, 1.9 Hz, 1H), 2.41–2.28 (m, 1H), 2.25–2.15 (m, 1H), 2.13–1.98 (m, 1H), 1.98–1.72 (m, 4H), 1.67–1.35 (m, 5H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.8, 139.3, 131.7, 129.2, 128.9, 48.96, 48.87, 45.0, 44.9, 32.1, 31.4, 30.3, 26.1, 23.6, 21.3, 14.9. HRMS: Calculated for $[C_{18}H_{25}OSe]^+$: 337.1065 [(M + H)$^+$]; found: 337.1066.

(3*S**,8*S**)-3,8-dimethyl-2,3,5,6,7,8-hexahydroazulen-4(1*H*)-one (**13**). To a solution of compound **11** (15.1 mg, 0.044 mmol) in in dry CH_2Cl_2 (0.7 mL) cooled at −78 °C was added MCPBA (15.5 mg, 0.09 mmol). The mixture was stirred for 60 min at this temperature and then a saturated solution of $NaHCO_3$ (5 mL) and CH_2Cl_2 (5 mL) were added. The phases were separated, washed with a saturated solution of $NaHCO_3$ (5 mL), dried over anhydrous Na_2SO_4, filtered and the solvent eliminated under reduced pressure affording the desired compound as a separable 1:2 mixture of **12**:**13** (8.0 mg, 0.044 mmol). The crude product was purified by flash column chromatography (petroleum ether/EtOAc 20:1) affording the major compound **13** (5.30 mg, 0.029 mmol) as a colorless oil. Yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16–3.02 (m, 1H), 2.76 (dtt, *J* = 18.1, 8.2, 1.6 Hz, 1H), 2.68–2.59 (m, 1H), 2.54 (dd, *J* = 7.3, 5.0 Hz, 2H), 2.34 (dddt, *J* = 17.9, 9.1, 3.8, 1.1 Hz, 1H), 2.03–1.70 (m, 4H), 1.64–1.48 (m, 1H), 1.40 (ddt, *J* = 12.2, 8.4, 3.6 Hz, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 160.8, 142.7, 44.3, 41.5, 36.8, 36.1, 34.2, 30.5, 20.1, 19.8, 19.8. HRMS: Calculated for $[C_{12}H_{18}O]^+$: 178.1358 [(M + H)$^+$]; found: 178.1365.

(3*S**,8*S**,8a*S**)-3a-bromo-3,8-dimethyloctahydroazulen-4(1*H*)-one (**14**). To a solution of compound **8** (18 mg, 0.10 mmol) in dry Et_2O (0.3 mL) at rt, NBS (18.7 mg, 0.105 mmol) and NH_4OAc (0.8 mg, 0.01 mmol) were added. The mixture was stirred at rt for 4 h. After this time, solids were filtered off and volatiles eliminated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/EtOAc gradient from 100:0 to 100:1) affording compound **14** (14.7 mg, 0.057. mmol) as a colorless oil. Yield: 57%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 (dddd, *J* = 12.7, 5.8, 4.8, 0.9 Hz, 1H), 2.60 (td, *J* = 10.1, 3.3 Hz, 1H), 2.55–2.45 (m, 1H), 2.30 (ddd, *J* = 12.7, 10.6, 5.2 Hz, 1H), 2.27–2.11 (m, 1H), 2.01–1.74 (m, 3H), 1.73–1.48 (m, 4H), 1.46–1.33 (m, 1H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 81.5, 57.2, 50.2, 42.9, 32.95, 29.9, 29.4, 23.9, 23.2, 21.4, 14.0. HRMS: Calculated for $[C_{12}H_{20}BrO]^+$: 259.0962 [(M + H)$^+$]; found: 259.0960.

(3*R*,8*S*,8a*R*)-3,8-dimethyloctahydroazulen-4(1*H*)-one (**16** and **16′**). To a solution of compound **3** (65 mg, 0.257 mmol) in dry Et_2O (1.0 mL) at 0 °C was added freshly prepared solution of Me_2CuLi in Et_2O (0.4 mL, 0.24 mmol, 0.6 *M*). The mixture was filtered through a short pad of Celite and then the solvent removed under reduced pressure. The crude

product was dissolved in EtOH (2 mL) and PtO_2 (15 mg, 0.066 mmol) was added. The mixture was exposed to an hydrogen atmosphere (1 atm with a balloon) for 5 h. The crude was evaporated and the desired compound was obtained as a separable 1:3 mixture of isomers **16** and **16′**, respectively (33 mg, 0.185 mmol). Combined yield: 73%. Purification by flash column chromatography afforded compound **16** and **16′** as a colorless oils. Data for isomer **16**: ^{1}H NMR (300 MHz, C_6D_6) δ 2.93–2.68 (m, 1H), 2.33–2.21 (m, 3H), 1.92–1.69 (m, 2H), 1.68–1.34 (m, 4H), 1.32–1.13 (m, 4H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 210.9, 63.6, 52.1, 44.1, 42.6, 37.8, 35.2, 32.1, 31.9, 22.5, 22.0, 20.3. HRMS: Calculated for $[C_{12}H_{21}O]^+$: 180.1587 [(M + H)$^+$]; found: 180.1577. Data for isomer **16′**: ^{1}H NMR (300 MHz, C_6D_6) δ 2.47–2.06 (m, 5H), 1.81 (dt, *J* = 12.5, 6.5 Hz, 1H), 1.60 (dt, *J* = 20.0, 8.4 Hz, 3H), 1.50–1.18 (m, 6H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 211.8, 64.2, 44.9, 42.5, 38.1, 35.9, 35.4, 34.0, 28.3, 23.8, 20.1, 18.6. HRMS: Calculated for $[C_{12}H_{21}O]^+$: 180.1587 [(M + H)$^+$]; found: 180.1579.

(3*R**,3a*S**,5*R**,8*S**,8a*R**)-5-(2-hydroxypropan-2-yl)-3,8-dimethyloctahydroazulen-4(1*H*)-one (**17**). To a freshly prepared solution of LDA in THF (0.45 mL) prepared using *i*Pr$_2$NH (56 µL, 0.399 mmol) and *n*-BuLi (0.195 mL, 0.33 mmol, 1.7 *M*) was added a solution of compound **16** (24.0 mg, 0.133 mmol) in THF (0.3 mL) at −78 °C. The reaction was stirred at this temperature for 1 h and then warmed to −40 °C. Then $ZnCl_2$ (0.23 mL, 0.16 mmol, 0.7 *M*) and dry acetone (0.110 mL, 1.46 mmol) were subsequently added. The reaction was stirred at −40 °C for further 1 h and then the mixture was treated with a saturated aqueous solution of NH_4Cl (5 mL) and Et_2O (5 mL) was added. The phases were separated, back extracted with Et_2O (2 × 5 mL) and the organic layers dried over anhydrous Na_2SO_4. Filtration and elimination of solvent afforded the crude product which was purified by flash column chromatography (petroleum ether/EtOAc gradient from 49:1 to 9:1) affording major compound **17** (18.3 mg, 0.077 mmol) as a white solid. Yield: 58%. ^{1}H NMR (300 MHz, C_6D_6) δ 2.95 (s, 1H), 2.86–2.70 (m, 1H), 2.46 (dd, *J* = 9.9, 9.9 Hz, 1H), 2.30 (dd, *J* = 12.3, 4.4 Hz, 1H), 1.92–1.60 (m, 4H), 1.59–1.43 (m, 1H), 1.27* (s, 3H), 1.27–1.14 (m, 4H), 1.14* (s, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 13C NMR (75 MHz, C6D6) δ 216.4, 72.4, 63.9, 63.8, 53.4, 42.5, 36.7, 36.3, 32.0, 31.8, 29.2, 27.4, 24.7, 21.7, 19.9. HRMS: Calculated for $[C_{15}H_{27}O_2]^+$: 239.2006 [(M + H)$^+$]; found: 239.2000.

(3*R**,3a*S**,5*R**,8*S**,8a*R**)-3,8-dimethyl-5-(prop-1-en-2-yl)octahydroazulen-4(1*H*)-one (**18**). A solution of compound **17** (116 mg, 0.486 mmol) and Burguess reagent (460 mg, 1.94 mmol) in toluene (25 mL) was heated under reflux. After 5 min the mixture was concentrated and the crude product was purified by flash column chromatography (petroleum ether/EtOAc gradient 19:1) affording compound **18** (93 mg, 0.42 mmol) as a colorless oil. Yield: 87%. ^{1}H NMR (300 MHz, C_6D_6) δ 4.95 (s, 1H), 4.91 (s, 1H), 3.04–2.90 (m, 1H), 2.77 (tt, *J* = 13.4, 4.5 Hz, 1H), 2.43 (dd, *J* = 10.2, 10.2 Hz, 1H), 1.97–1.81* (m, 2H), 1.82* (s, 3H), 1.79–1.56 (m, 3H), 1.43–1.08 (m, 5H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6) δ 210.3, 144.0, 111.5, 61.6, 61.3, 54.2, 42.9, 36.0, 36.0, 32.0, 32.0, 28.1, 22.7, 21.8, 19.4. HRMS: Calculated for $[C_{15}H_{25}O]^+$: 221.1900 [(M + H)$^+$]; found: 221.1901.

(3*R**,3a*S**,5*R**,8*S**,8a*R**)-3,8-dimethyl-5-(prop-1-en-2-yl)decahydroazulen-4-ol (**19** and **19′**). To a solution of compound **18** (74 mg, 0.33 mmol) in CH_2Cl_2 (6 mL) at −78 °C, a solution of DIBAL-H (1.00 mL, 1.00 mmol, 1 *M*) was added. The mixture was stirred for 5 min at this temperature and then quenched with a H_2O (5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated, the organic dried over anhydrous Na_2SO_4, and filtration and elimination of solvent afforded the crude product which was purified by flash column chromatography (petroleum ether/EtOAc 19:1) affording major compound **19** (43.3 mg, 0.19 mmol) and **19′** (18 mg, 0.080) as a colorless oil. Combined yield: 81%. Data for isomer **19**: ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates partially overlapped resonances) δ 5.01 (s, 1H), 4.74 (s, 1H), 3.59 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.24 (dd, *J* = 9.8, 4.2 Hz, 1H), 2.10–1.93 (m, 1H), 1.93–1.70 (m, 7H), 1.69–1.55 (m, 1H), 1.54–1.18 (m, 6H), 1.10–0.94* (m, 1H), 1.06* (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 5.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 112.7, 74.6, 58.4, 52.4, 48.6, 42.1, 41.9, 40.8, 33.1, 31.7, 25.8, 23.5, 23.1, 21.9. Calculated for $[C_{15}H_{27}O]^+$: 223.2056 [(M + H)$^+$]; found: 223.2065. Data for isomer **19′**: ^{1}H NMR (300 MHz, $CDCl_3$) δ

4.77 (s, 1H), 4.72 (s, 1H), 3.79 (dt, *J* = 7.1, 3.5 Hz, 1H), 2.16–1.99 (m, 2H), 1.92–1.61 (m, 7H), 1.61–1.50 (m, 2H), 1.49–1.33 (m, 3H), 1.32–1.08 (m, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 110.7, 71.3, 57.1, 56.0, 44.5, 42.0, 39.8, 36.6, 33.6, 30.8, 28.7, 22.1, 20.3, 19.2. HRMS: Calculated for $[C_{15}H_{27}O]^+$: 223.2056 $[(M + H)^+]$; found: 223.2049.

(4*R**,5*S**)-1-*epi*-11,12-didehydro-4,5-dihydroisoguaiene. To a solution of compound **19** (30 mg, 0.134 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added the Martin sulfurane (270 mg, 0.40 mmol) dissolved in CH_2Cl_2 (1 mL). The mixture was stirred for 2 h and then the crude product concentrated and purified by flash column chromatography (petroleum ether) affording the title compound (27.3 mg, 0.13 mmol) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) (* indicates partially overlapped resonances) δ 5.78 (d, *J* = 4.3 Hz, 1H), 5.00 (d, *J* = 1.4 Hz, 1H), 4.85 (s, 1H), 2.53 (dd, *J* = 14.9, 7.8 Hz, 1H), 2.28–2.18 (m, 1H), 1.90* (s, 3H) 1.89–1.65* (m, 4H), 1.51–1.41 (m, 1H), 1.36–1.11 (m, 6H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 144.2, 132.1, 110.2, 52.5, 51.3, 43.9, 42.0, 34.6, 32.2, 31.0, 27.7, 22.2, 21.4, 19.6. HRMS: Calculated for $[C_{15}H_{25}]^+$: 205.1951 $[(M + H)^+]$; found: 205.1953.

4. Conclusions

The transannular Morita-Baylis-Hillman reaction using racemic chiral medium-sized cyclic ketoenone **1** under kinetic resolution conditions is a good approach to enantiopure 10-methyl substituted functionalized decahydroazulene derivatives. This reaction has been optimized and applied to the generation of the central core of guaiane and aremadendrane families of sesquiterpenoids. The enantioenriched MBH adduct has been used as starting material for the preparation of several sesquiterpene-related compounds such as γ-Gurjunene, Clavukerin A, non-natural *1-epi-11,12-didehydro-4,5-dihydroisoguaiane* and an advanced intermediate in the synthesis of Palustrol.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal12010067/s1, Figures S1–S11: NMR spectra of new compounds.

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