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Chemistry of odorants: stereoselective synthesis of octahydronaphthalene-based perfumery *Georgywood*, (+,−)-1-[(1*R* *,2*S* *)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one

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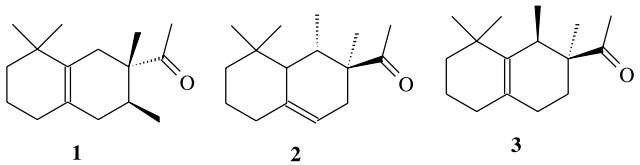
Abstract—A straightforward synthesis of octahydronaphthalene-based fragrance, such as *Georgywood*, is described. The Lewis acid tin (IV) chloride catalyzed efficiently an original one-pot sequential cycloaddition–clyclization process by reaction of myrcene with 3-bromo-but-3-en-2-one, leading directly to the octahydronaphthalene skeleton in very good yields (85%). Then, dehydrohalogenation with DBU gave the key 2,4-dienone intermediate in excellent yield (85%). Regioselective Michael addition gave rise to the formation of the addition product as a *trans*/*cis* diastereoisomeric mixture, by reaction either with $CH_3Cu{\cdot}BF_3$ (6:1 ratio, 70%) or $(CH_3)_2CuLi$/TMSCl reagents (3:1 ratio, 80%). The generation of thermodynamically more stable enolate by treatment of the diastereoisomeric mixture with sodium hydride in tetrahydrofuran in the presence of an excess of methyl iodide, allowed stereoselective introduction of the methyl group at C2, leading to the formation of *Georgywood* in good yield (60%), as the only diastereoisomer, with a *trans* stereochemistry of the two methyl groups as demonstrated by NMR experiments.

1. Introduction

The octahydronaphthalene skeleton constitutes a structural requirement of industrially significant fragrances, such as *Iso E Super*® **1**, its powerful minor constituent **2**, and *Georgywood* **3** (Fig. 1).[1] All the compounds fulfil the above structural requirements, possessing a rich, warm-woody odor with a shade of amber.[2] The industrial synthesis of **1** starts with the aluminium trichloride catalyzed Diels–Alder reaction of myrcene with (3*E*)-3-methylpent-3-en-2-one, followed by a cyclization reaction of the substituted cyclohexene intermediate in presence of sulfuric acid, which leads to **1**. Surprisingly, it was found that it is not the main component **1** but ca. 5% constituent **2** that determines the woody-amber odor of commercially *Iso E Super*® **1**.[3] The formation of **2** as a by-product during the synthesis of **1** was rationalized by an acid-catalyzed rearrangement of olefinic intermediates. As a consequence, numerous structural analogues of **2** were synthesized, of which *Georgywood* **3** was found to be one of best, showing the same odor threshold and possessing a very attractive warm-woody, sweet-powdery smell.[4]



1 2 3

Figure 1. Structures of compounds **1**, **2** and **3**.

The strategy for the synthesis of *Georgywood* **3** includes the well-known and previously described two step sequence: first, the Lewis acid-activated Diels–Alder reaction of homomyrcene[5] with methyl isopropenyl ketone, then the subsequent acid-catalyzed cyclization of the cyclohexene intermediate to **3**.[5] In this publication, we report a new synthesis of octahydronaphthalene-type odorants, such as **3**, by a general strategy which should make the bicyclic intermediates synthetically more accessible. It was our particular aim to find a simplified synthetic strategy, and to be guided by readily available starting materials in conjunction with straightforward chemistry.

Keywords: Odorants; *Georgywood*; Diels–Alder reactions; Octahydronaphthalene skeleton; Lewis acid mediated conjugate addition.
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2. Results and discussion

2.1. Synthesis of octahydronaphthalene skeleton

Our strategy commenced with the construction of the octahydronaphthalene skeleton. We had in mind to find a protocol, which should easily access the bicyclic framework through a one-pot process. This goal was addressed performing an original domino sequence by a tin (IV) chloride-catalyzed Diels–Alder reaction of myrcene **4** with 3-bromo-but-3-en-2-one **5**. The reaction was carried out in CH_2Cl_2 at −78 °C, and we observed the direct formation of the desired ethanone,1-(2-bromo-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl) **6** as the only regioisomer in 85% yield (Scheme 1) (Table 1, entry 5). The outcome of the reaction can be explained first with a $SnCl_4$ oriented Diels–Alder reaction,[6,7] immediately followed by an intramolecular cyclization of the unsaturated cyclohexene intermediate, such as **7**, to give **6**.[8,9] To the best of our knowledge, there are no examples of the direct synthesis of such molecules by a $SnCl_4$-guided one-pot sequential cycloaddition–cyclization process.[1]

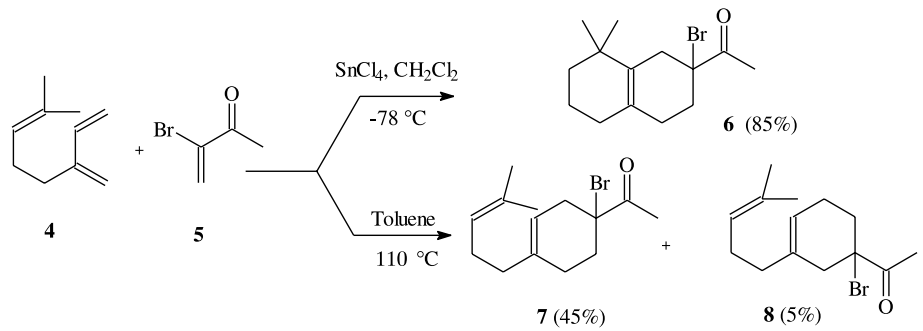
It is worth noting that the thermal uncatalyzed cycloaddition of myrcene with methyl vinyl ketone is described to give rise to a mixture of two regioisomeric cyclohexene derivatives.[8b,10]

However, when the reaction was carried in toluene at 25 °C and with $SnCl_4$ as catalyst, a mixture of the two regioisomeric cycloaddition adducts **7** and **8** was obtained, with a 80:20 ratio and a 50% yield (Table 1, entry 4). The use of a different Lewis acid as catalyst, such as $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 25 °C, gave a mixture of the two regioisomers **7** and **8**, with a 80:20 ratio and a poor yield (25%) (Table 1, entry 3).[11] The results show that tin (IV) chloride plays a pivotal role. Probably, the donor–acceptor interaction between the dienophile and the catalyst lowers the LUMO energy of the dienophile, favoring the stabilization of a sterically less crowded *endo* transition state.[12] As a consequence, the Lewis acid catalyzed cycloaddition proceeded faster and more regioselectively than the thermal counterpart, giving first the monocyclic adduct,[6,12] such as **7**, then promoting the intramolecular cyclization reaction to the octahydronaphthalene derivative **6**. The capability of tin (IV) chloride to act as promoter of intramolecular cyclization reactions has been described many times. For instance, Saito,[9a,b] Kawanobe and co-workers[9c] studied the $SnCl_4$-mediated cyclization of both homofarnesoic acid and monocyclo homofarnesoic acid to racemic sclareolide. Furthermore, the formation of any regioisomeric octahydronaphthalene derivative, such as **9** (Fig. 2), was never detected according to the above experimental procedure.

Performing the uncatalyzed cycloaddition process, toluene was needed as solvent and higher temperatures were required: at 60 °C, the regioisomeric cyclohexene derivative **7** was obtained with a 30% yield, while at 110 °C the two regioisomers **7** and **8** were formed with a 50% yield and a 90:10 ratio (Scheme 1) (Table 1, entries 1 and 2, respectively). Moreover, the formation of octahydronaphthalene derivatives, such as **6**, was never detected under these experimental conditions. Finally, **7** was cyclized with concentrated sulfuric acid into the corresponding octahydronaphthalene skeleton **6**, in agreement with the regiochemistry of the cycloaddition reaction.[8b,10]

2.2. Dehydrohalogenation

The next step was the dehydrohalogenation of **6** to get 1-(8,8-dimethyl-3,4,5,6,7,8-hexahydronaphthalen-2-yl)ethan-1-one **10**. The elimination reaction was efficiently carried out by treatment **6** with DBU in CH_2Cl_2 as solvent at 0 °C, 24 h;[8b,10a] the 2,4-dienone **10** was obtained with a 85% yield. The same reaction on **7** led to 1-[4-(4-methyl-3-

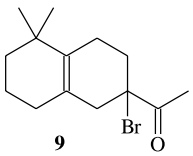


Scheme 1. Synthesis of **6**, **7** and **8**.

Table 1. The Diels–Alder reaction of myrcene **4** with 3-bromo-pent-2-en-3-one **5**

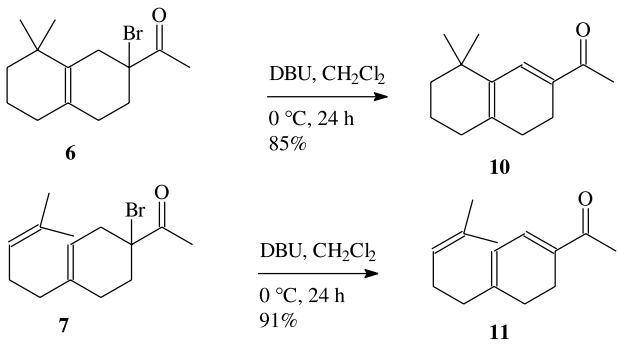
Entry	Catalyst (equiv.)	Solvent	Reaction time (h)	Temperature (°C)	Products	Yield (%)	Ratio[a]
1	—	Toluene	24	60	**7**	30	100:0
2	—	Toluene	48	110	**7**+**8**	50	90:10
3	$BF_3{\cdot}OEt_2$ (0.1)	CH_2Cl_2	1	25	**7**+**8**	25	80:20
4	$SnCl_4$ (0.1)	Toluene	1	0	**7**+**8**	50	80:20
5	$SnCl_4$ (0.3)	CH_2Cl_2	4	−78	**6**	85	100:0

[a] Determined by GC-MS analysis.



9

Figure 2. Structure of compound **9**.



6 10

7 11

Scheme 2. Synthesis of **10** and **11**.

pentenyl)-1,3-cyclohexadienyl]ethan-1-one **11** with a 91% yield.(Scheme 2).

Other reagents, such as Al_2O_3 or pyridine, gave poor yields of **10**.

2.3. Conjugate addition

Activated 2,4-dienones, such as **10** and **11**, can provide several isomeric products in copper-mediated Michael addition reactions. Besides direct nucleophilic attack at the carbonyl group, **10** and **11** can undergo 1,4 or 1,6-addition, giving rise to a mixture of three regioisomeric substituted cycloalkenes which contain new stereogenic centers.[13] As a consequence, the major challenge was control of the regio- and stereoselectivity of the Michael addition.[13c]

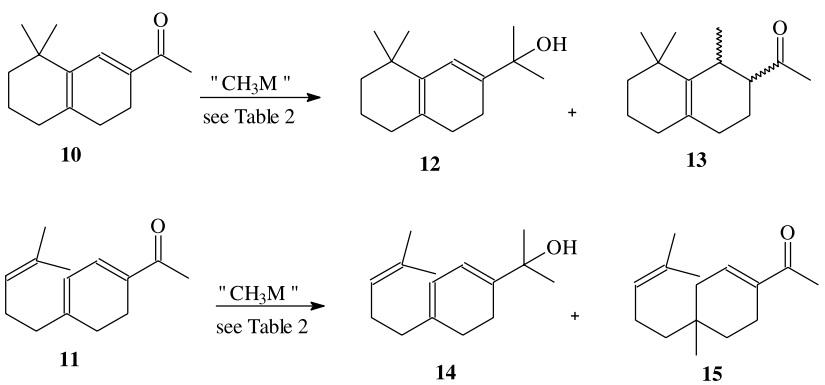
Thus, many different combinations of copper(I) salts, organometallic compounds and solvents have been employed to study the reactivity, the efficiency and the selectivity of the 2,4-dienones as Michael acceptor for the introduction of a methyl group at C1 of **10** and at C2 of **11**.(Table 2).

It was found that under the conditions usually employed for metallo-assisted 1,4-Michael additions,[16] i.e. by treatment with the Grignard reagent, with or without copper (I) salts as catalyst,[13,16] (Table 1, entries 1, 2, 3 and 6), dimethyl-lithiumcuprate (entries 4 and 5), methyl lithium and HMPT or DMPU as co-solvents (entries 7 and 8),[17] methyl lithium and cumene (entries 9 and 10),[18] both dienones **10** and **11** were almost unreactive and the 1,4-Michael addition reactions proceeded unsuccessfully. We observed the

Table 2. Michael addition to 2,4-dienones **10** and **11**

Entry	Substrate	Reagent (equiv.)	Solvent	Temperature (°C)	Product (yield, %)[a]
1	**10**	CH_3MgCl (1)[14,15]	THF	−78	**12** (40)
2	**11**	CH_3MgCl (1)[15,16]	Et_2O	−78	**14** (tr), **15** (tr)
3	**10**	$(CH_3)_2CuMgCl$	THF	−78	**12** (15), **13** (tr)
4	**11**	$(CH_3)_2CuLi$ (1.5)	Et_2O	−78	**15** (tr)
5	**10**	$(CH_3)_2CuLi$ (1)[15]	THF	−78	—
6	**10**	CH_3MgCl (3), CuI (0.05)	Et_2O	−78/0	**12** (tr), **13** (tr)
7	**10**	CH_3Li (1) HMPT[17]	*n*-Hexane	−78	**12** (tr)
8	**10**	CH_3Li (1.5) DMPU	*n*-Hexane	−78	—
9	**10**	CH_3Li·cumene (1)[18]	THF	−78	**12** (tr)
10	**10**	CH_3Li·cumene. (1) HMPT[18]	THF	−78	**12** (tr), **13** (tr)
11	**11**	$CuCH_3{\cdot}BF_3$ (6)	Et_2O	−78	**15** (65)
12	**10**	$CuCH_3{\cdot}BF_3$ (1)	Et_2O	−78	**13** (15)
13	**10**	$CuCH_3{\cdot}BF_3$ (3)	Et_2O	−78	**12** (12), **13** (40)
14	**10**	$CuCH_3{\cdot}BF_3$ (6)	Et_2O	−78	**12** (24), **13** (70)
15	**10**	$(CH_3)_2CuLi$. TMSCl (3)[19]	Et_2O	−78	**12** (15), **13** (80)

[a] Determined by GC-MS analysis.



10 12 13

11 14 15

Scheme 3. Synthesis of **13** and **15**.

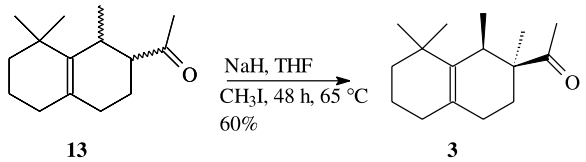
formation of the 1,2-adduct **12** in poor yields (entries 1 and 2) (Scheme 3).

In recent past years, Yamamoto described the Lewis acid-mediated reactions of organocopper reagents with various kinds of α,β-unsaturated carbonyl compounds.[20] Particularly, RCu·BF_3 has found favor as a valued Michael donor in couplings with α,β-γ,δ-unsaturated ketones, esters, and even acids.[21] As reported, methyl sorbate undergoes a 1,4-addition via BuCu·BF_3, while undergoing a 1,6-α,δ-addition via Bu_2CuLi.[22] Prompted by these findings, we exploited the reactivity of the Yamamoto's reagent ($CH_3Cu·BF_3$) with the dienones **10** and **11** (Scheme 3). Actually, the 2,4-dienone **11** reacted with the Yamamoto's reagent to provide with complete 1,6-regioselectivity the enone **15** in 65% yield (entry 11). On the other hand, the reaction of the 2,4-dienone **10** with $CH_3Cu·BF_3$ gave preferentially the desired 1,4-adduct **13**, together with small quantities of 1,2-adduct **12** as a side-product (entries 12, 13 and 14).[15b] Surprisingly, the enone **10** was unreactive as a 1,6-Michael acceptor, probably due to the sterically more crowded γ,δ-double bond. The best yields were obtained with a 1:6 substrate/reagent ratio (entry 14). Furthermore, by treatment with dimethyl lithium cuprate activated with TMSCl as a soft Lewis acid, the dienone **10** provided the desired enone **13** in good yield (80%), while the formation of the side-product **12** decreased.[19,23] The enone **13** was obtained as an inseparable diastereoisomeric mixture, the diastereoselectivity varying from 6:1 to 3:1 *trans*/*cis* ratio with Yamamoto's reagent and with $(CH_3)_2CuLi$/TMSCl reagent, respectively.[24] The stereochemistry of the two diastereoisomers was established by ^1H NMR analysis: *trans* isomer: CH_3 at C1, 0.87 δ, d (J=6.6 Hz); CH_3CO, 2.17 δ, s; H_a–C1/H_b–C2, J=11.0 Hz, in agreement with a *trans*–*anti* relationship; *cis* isomer: CH_3 at C1, 1.17 δ, d (J=6.6 Hz); CH_3CO, 2.13 δ, s, in agreement with their *cis* relationship.[20b]

It is worth noting that octahydronaphthalene derivatives, such as **13**, are valuable compounds in the chemistry of fragrances.[5b] Furthermore, the results show the flexibility of our strategy, allowing to prepare a library of differently C1 alkyl-substituted octahydronaphthalenes by reaction of the dienone **10** with suitable organocopper reagents, such as RCu·BF_3 or R_2CuLi/TMSCl.

2.4. Synthesis of (+,−)-1-[(1*R**,2*S**)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl)ethan-1-one, *Georgywood*, 3

All the experiments for a one-pot sequential alkylation of the ketone enolate generated by organo copper conjugate addition failed, both utilizing CH_3I or CH_3OTf as electrophiles and HMPA as co-solvent.[25] To overcome this limitation, the introduction of a methyl group at C2 was successfully addressed by performing the alkylation reaction directly on the diastereoisomeric mixture **13**. The conversion was performed through the generation of thermodynamically more stable enolate with sodium hydride in tetrahydrofuran in the presence of an excess of methyl iodide,[26] leading to the formation of **3** in 60% yield, as the only diastereoisomer (Scheme 4). Interestingly, the alkylation reaction was completely diastereoselective,



13 **3**

(*trans*/*cis* diastereoisomeric mixture)

Scheme 4. Synthesis of *Georgywood* **3**.

giving rise to the formation of only the compound **3**. By GC co-injection and NMR spectra, the synthetic material **3** proved to be totally identical with an authentic sample of the well-known fragrance *Georgywood*.[5b,c]

3. Conclusion

We have demonstrated that the octahydronaphthalene skeleton can be directly and readily achieved in high yields and regioselectivity by an original tin (IV) chloride-catalyzed domino process, characterized by a sequence of an intermolecular oriented Diels–Alder reaction, immediately followed by an intramoleculr cyclization to give the bicyclo compound. This new procedure leading to the bicyclo skeleton shortened the previously reported two-step sequences. The key-intermediate, the 2,4-dienone **10**, gave an excellent performance in regio- and stereoselective double alkylation reactions, making the target compound easily available. Therefore, these new transformations can be efficiently utilized in target-oriented syntheses.

Finally, the results show the good flexibility of our strategy, which allows preparation of a library of differently alkyl-substituted octahydronaphthalenes, valuable in the chemistry of odorants. Future research in this area will concentrate on the further development of new catalytic and enantioselective transformations.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures and kept over a drying agent before use. Organometallic compounds were prepared or purchased as previously described.[27] Other reagents were purchased from commercial suppliers and were used without purification. Analytical TLC was performed using silica gel 60 F_{254} plates (Merck) and detected by treatment with a solution of H_2SO_4 2 N. Column chromatography was performed using silica gel 60 (0.063–0.200 nm) (Merck) and flash chromatography using silica gel 60 (0.040–0.063) (Merck). GC-MS analyses were performed with Hewlett–Packard GC 5890 coupled with Hewlett–Packard MS 5971A and Hewlett–Packard PC 9000. IR spectra were recorded on IR-470 infrared spectrophotometer Shimadzu. HRMS spectra were recorded with Micromass Q-TOF *micro* Mass Spectrometer (Waters). ^1H NMR and ^{13}C NMR were recorded on a VARIAN GEMINI 200 MHz spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent and as internal standard, unless stated otherwise. All chemical shifts are expressed in parts per million relative to $CDCl_3$

(δ=7.27). Spin–spin coupling constants in Hz (J) were measured directly from the spectra. The assignment of peaks in the ^{13}C NMR spectra was made by APT experiments.

4.1.1. 1-(2-Bromo-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl)ethan-1-one, 6. 3-Bromo-but-3-en-2-one **5**[28] (2.1 g, 14 mmol) in dry CH_2Cl_2 (40 mL) was stirred with $SnCl_4$ (1.08 g, 0.41 mmol), at −78 °C under argon for 30 min, then myrcene (1.9 g, 14 mmol) was added dropwise and the reaction mixture was stirred for 4 h and then was allowed to warm up to room temperature. The organic solution, washed with water (2×10 mL), saturated aqueous solution $NaHCO_3$ (2×10 mL) and water (10 mL) until neutrality, brine (5 mL) and dried over anhydrous Na_2SO_4, was concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate 9/1) to give **6** as viscous oil (3.39 g, yield 85%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1715, 1371, 1358, 1217, 1111. ^1H NMR (δ, $CDCl_3$): 2.80–2.57 (1H, m); 2.41 (3H, s); 2.29–2.10 (4H, m); 1.85 (2H, m); 1.68–1.54 (3H, m); 1.49–1.44 (2H, m); 1.0 (6H, s). ^{13}C NMR (δ, $CDCl_3$): 211.2 (C=O); 131.9, 126.2 (C quat); 68.5 (C–Br); 39.4; 36.1 (C quat); 33.7; 32.9; 26.8; 26.9; 24.1; 20.9; 19.9. HRMS calcd for $C_{14}H_{21}$ ^{79}BrO $[M+NH_4]^+$ 302.0776, found 302.0778.

4.1.2. 1-[1-Bromo-4-(4-methyl-3-pentenyl)-3-cyclohexenyl]ethan-1-one, 7 and 1-[1-Bromo-3-(4-methyl-3-pentenyl)-3-cyclohexenyl]ethan-1-one, 8. A stirred solution of 3-bromo-but-3-en-2-one **5** (2.1 g, 14 mmol) and myrcene (1.9 g, 14 mmol) in dry toluene (20 mL) was heated under reflux. After 48 h, the reaction mixture was cooled to room temperature and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and washed with water (10 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash chromatography (hexane/ethyl acetate 20/1) to give **7** (1.8 g, yield 45%) and **8** (200 mg, yield 5%), both as viscous oils.

Compound **7**. IR ν_{max} ($CHCl_3$)/cm^{-1}: 1714, 1361, 1215, 1109. ^1H NMR (δ, $CDCl_3$): 5.25 (1H, m); 5.01 (1H, m); 2.81–2.58 (2H, m); 2.35 (3H, s); 2.24–1.93 (8H, m); 1.62 (3H, s); 1.54 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 196.1 (C=O); 147.1; 131.1, 123.5 (Cquat); 122.5; 69.1 (CBr); 39.0; 36.1; 33.7; 33.1; 30.1; 27.5; 27.2; 19.0. HRMS calcd for $C_{14}H_{21}^{79}BrO$ $[M+NH_4]^+$ 302.0776, found 302.0777.

Compound **8**. IR ν_{max} ($CHCl_3$)/cm^{-1}: 1713, 1358, 1217, 1110. ^{13}C NMR (δ, $CDCl_3$): 195.5 (C=O); 143.3; 133.7, 123.9 (Cquat) 123.0; 67.2 (CBr); 39.8; 38.4; 33.6; 33.1; 29.6; 27.5; 27.3; 19.1. HRMS calcd for $C_{14}H_{21}^{79}BrO$ $[M+NH_4]^+$ 302.0776, found 302.0779.

Compound **7** (0.2 g) was dissolved in toluene (5 mL) and was added dropwise to 0.7 g of a 60% H_2S0_4 ice-cooled solution. The yellow solution was then stirred at 40 °C. After 2 h, the organic layer was washed with water (2×10 mL), saturated bicarbonate solution (3×10 mL), brine (2×5 mL), dried over Na_2SO_4 and concentrated in vacuo to give a crude product that was purified by flash chromatography (hexane/ethyl acetate 9/1) to provide **6** (140 mg, yield 70%).

4.1.3. 1-(3,4,5,6,7,8-Hexahydro-8,8-dimethyl-2-naphthalenyl)ethan-1-one, 10. To a stirred solution of **6** (1.0 g, 3.5 mmol) in dry CH_2Cl_2 (5 mL), DBU (1.06 g, 7.0 mmol) was added dropwise at 0 °C under argon. After 24 h, the organic layer was washed with a saturated aqueous solution of $CuSO_4$ (until blue color disappeared), water (10 mL), brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo to give a crude product that was purified by flash chromatography (hexane/ethyl acetate 20/1) to provide **10** as viscous oil (610 mg, yield 85%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1680, 1630, 1360, 1210, 1111. ^1H NMR (δ, $CDCl_3$): 7.04 (1H, s); 2.33 (3H, s); 2.12–2.07 (4H, m); 1.70–1.58 (3H, m); 1.53–1.48 (3H, m); 1.06 (6H, s). ^{13}C NMR (δ, $CDCl_3$): 198.3 (C=O); 139.5, 134.8, 134.5 (C quat); 135.5; 38.9; 32.5 (C quat); 31.5; 29.3; 28.6; 25.1; 20.2; 19.1. HRMS calcd for $C_{14}H_{20}O$ $[M+NH_4]^+$ 222.1514, found 222.1517.

4.1.4. 1-[4-(4-Methyl-3-pentenyl)-1,3-cyclohexadienyl]ethan-1-one, 11. Compound **7** (1.0 g, 3.5 mmol) and DBU (1.06 g, 7.0 mmol), under the same reaction conditions and purification to prepare **10**, gave **11** as viscous oil (651 mg, yield 91%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1680, 1640, 1369, 1217, 1110. ^1H NMR (δ, $CDCl_3$): 6.83 (1H, d, J=6.1 Hz); 5.79 (1H, d, J=6.1 Hz); 5.02 (1H, m); 2.37 (1H, m); 2.32 (1H, m); 2.23 (3H, s); 2.15 (1H, s); 2.12 (5H, m); 1.61 (3H, s); 1.53 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 198.1 (C=O); 150.2; 135.3; 134.0; 132.2; 123.5; 118.9; 37.6; 27.5; 26.0; 25.7; 25.0; 20.4; 17.7. HRMS calcd for $C_{14}H_{20}O$ $[M+NH_4]^+$ 222.1514, found 222.1519.

4.1.5. 1-(1,2,3,4,5,6,7,8-Octahydro-1,8,8-trimethyl-naphthalen-2-yl]ethan-1-one, 13 (as inseparable *trans*/*cis* diastereoisomeric mixture). *Method a*. (Yamamoto's reagent) CuI (570 mg, 3.0 mmol) in dry Et_2O (5 mL) was treated dropwise with a 1.5 M THF solution of MeLi (2 mL, 3.0 mmol, 1) under argon at 0 °C. Then $BF_3{\cdot}Et_2O$ (0.4 mL, 3.0 mmol) was added dropwise at −78 °C and stirred. After 20 min, **10** (102 mg, 0.5 mmol), in 2 mL of dry Et_2O, was added under stirring. After 30 min, aqueous NH_4Cl/NH_3 solution (4 mL) was added and the mixture extracted once with ethyl acetate (50 mL). The organic layer was washed with water (10 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a light-yellow oil that was purified by flash chromatography (hexane/ethyl acetate 20/1) to provide **13** as viscous oil (78 mg, yield 70%) as an inseparable 6:1 *trans*/*cis* diastereoisomeric mixture, as shown by NMR spectra. IR ν_{max} ($CHCl_3$)/cm^{-1}: 1713, 1358, 1217, 1110. ^1H NMR (*trans*/*cis* mixture) (δ, $CDCl_3$): 2.68 (C*H*, m); 2.38 (C*H*, dt, J=6.6, 11.0 Hz); 2.17 (CH_3CO, s); 2.13 (CH_3CO, s); 1.9–1.3 (10H, m); 1.17 (CH_3CH, d, J=6.6 Hz); 1.08 (2×CH_3, s); 1.06 (CH_3, s), 1.02 (CH_3, s); 0.87 (CH_3CH, d, J=6.6 Hz). ^{13}C NMR (*trans*/*cis* mixture) (δ, $CDCl_3$): (*trans*) 211.2 (C=O); 139.9, 127.2 (Cquat); 53.4; 40.4; 34.6; 31.0; 29.9; 29.9; 29.6; 28.4; 23.0; (*cis*) 210.3; 137.1, 127.0 (C quat); 54.8; 40.7; 33.9; 31.3; 29.4; 27.9; 27.6; 23.0. HRMS calcd for $C_{15}H_{24}O$ $[M+NH_4]^+$ 238.1827, found 238.1825.

Method b. To a cold (−78 °C) solution of dimethyl lithium cuprate (2.0 mmol) in 5 mL of dry ether, freshly distilled

trimethylchlorosilane (0.25 mL, 2.0 mmol) was added dropwise under stirring. After 1 h, **10** (102 mg, 0.5 mmol), in 2 mL of dry Et_2O, was added under stirring. After 1 h, the reaction mixture was allowed to warm up to room temperature. The usual work up as previously described furnished 88 mg of **13** (yield 80%) as an inseparable 3:1 *trans*/*cis* diastereoisomeric mixture.

In both methods, the formation of **12** as viscous oil and as a side product derived from 1,2-addition was detected, with a variable yield (method a: 24%; method b: 15%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 3370, 1660, 1358, 1110. ^1H NMR (δ, $CDCl_3$): 5.93 (1H, s), 2.25–1.95 (6H, m), 1.70–1.40 (4H, m), 1.42 (6H, s), 1.08 (6H, s). ^{13}C NMR (δ, $CDCl_3$): 138.9, 134.2, 128.4 (Cquat), 120.2, 77.0 (Cquat), 39.4; 32.2; 31.3; 29.7; 28.1; 25.2; 22.1; 19.7. HRMS calcd for $C_{15}H_{24}O$ $[M+NH_4]^+$ 238.1827, found 238.1830.

4.1.6. 1-[4-Methyl-4-(4-methyl-3-pentenyl)-1-cyclohexenyl]ethan-1-one, 15. Compound **11** (102 mg, 0.5 mmol), under the same reaction conditions and purification to prepare **13** (method a), gave **15** as oil (72 mg, yield 65%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1685, 1660, 1358, 1210, 1111. ^1H NMR (δ, $CDCl_3$): 6.82 (1H, m); 5.08 (1H, m); 2.28 (3H, s); 2.23 (1H, m); 2.04 (2H, m); 1.95 (2H, m); 1.67 (3H, s); 1.59 (3H, s); 1.42 (2H, m); 1.24 (2H, m); 0.88 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 193.0 (C=O); 139.5, 126.4 (Cquat); 124.8; 122.1; 49.0; 43.1; 42.1; 37.3; 32.8; 27.5; 25.8; 21.9; 17.8. HRMS calcd for $C_{15}H_{24}O$ $[M+NH_4]^+$ 238.1827, found 238.1825.

4.1.7. (+,−)-1-[(1*R,2*S**)-1,2,3,4,5,6,7,8-Octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one, *Georgywood*, 3.** A *trans*/*cis* mixture of **13** (160 mg, 0.72 mmol) was dissolved in dry THF (10 mL) under argon at 0 °C, then NaH (70 mg, 2.9 mmol) and CH_3I (750 mg, 5.28 mmol) were added. The reaction mixture was allowed to warm up to room temperature, then to reflux for 48 h. The reaction mixture, diluted with Et_2O (50 mL), was treated with MeOH (0.5 mL), then washed, water (5 mL) until neutrality, brine (3 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuum and the product was purified by flash chromatography (hexane/ethyl acetate 20/1) to give the fragrant oil, *Georgywood*, **3**, as viscous oil and as only one diastereoisomer (101 mg, yield 60%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 2928, 2832, 1702, 1459, 1376, 1357, 1239, 1219, 1195, 1126, 1090, 1065, 1028, 964. ^1H NMR (δ, $CDCl_3$): 2.36 (1H, q); 2.15 (3H, s); 2.1–1.7 (6H, m); 1.55–1.4 (4H, m); 1.06 (3H, s); 1.02 (3H, s); 0.99 (3H, s); 0.86 (3H, d, J=6.6 Hz). ^{13}C NMR (δ, $CDCl_3$): 214.4 (C=O); 136.9, 125.9 (C=C); 50.7 (C2 q); 40.1; 35.4 (C1); 34.0 (C8 q); 30.8; 29.4, 28.4 (CH_3); 27.6; 24.8 (CH_3); 22.5; 21.0, 19.7 (CH_3); 19.1. HRMS calcd for $C_{16}H_{26}O$ $[M+NH_4]^+$ 252.1984, found 252.1988.

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