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Enantioselective synthesis of (+)-α-vetivone through the Michael reaction of chiral imines

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Abstract

(+)-α-Vetivone has been synthesised in nine steps. The absolute stereochemistry of the two stereogenic centres is controlled in the same key step involving the stereoselective Michael addition of a chiral imine of 4-isopropylidene-2-methylcyclohexanone to phenyl crotonate.

1. Introduction

The enantioselective Michael addition of chiral imines[1] has been widely used for synthetic purposes, in particular to sesquiterpenes such as geosmin.[2] The reaction has also proved to be applicable to α- or β-substituted electrophilic olefins.[1e] In this case, Michael adducts bearing two stereogenic centres are obtained in high enantio- and diastereoselectivities. With a β-methyl electrophilic olefin and an appropriate chiral 2-methylcyclohexanone imine, the method can therefore constitute a straightforward asymmetric route to sesquiterpenes bearing two vicinal methyl groups. This approach has already been illustrated in our laboratory by the enantioselective synthesis of a chiral building block useful for the preparation of valancane derivatives, and (+)-valancenol has been synthesised.[3]

More than 60 years ago, Pfau and Plattner isolated from vetiver oil (*Vetiveria zizanioides* Stapf) its most important odoriferous constituent which they named α-vetivone.[4] The structure of the compound, belonging to the eremophilane group of sesquiterpenoids, was established about 30 years later independently by de Mayo[5] and Marshall.[6] Syntheses of racemic α-vetivone[7–9] as well as a hemi-synthesis of (+)-α-vetivone from (−)-β-pinene[10] have been reported but no enantioselective synthesis has been achieved so far.

2. Results and discussion

We report here a short synthesis of (+)-α-vetivone **11** which required the preparation of chiral

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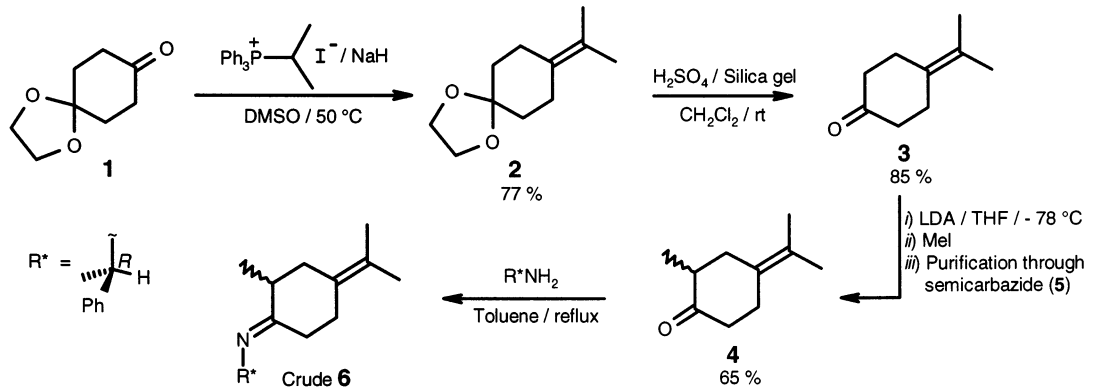
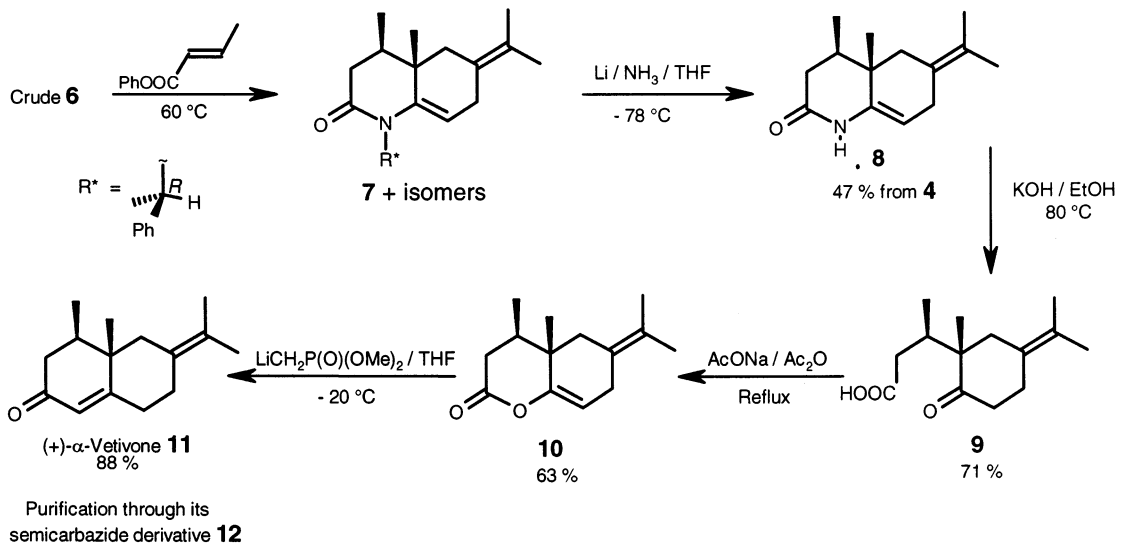
imine **6**. This compound was obtained in four steps from the commercial monoprotected dione **1**. Wittig reaction led to ethylenic compound **2** in 77% yield. After attempting deprotection of the ketonic function of **2** using several conditions, the best result was observed when following Conia's procedure[11] which led to ketone **3** and unreacted starting material **2** (85% yield calculated for a 89% conversion). Subsequent alkylation under classical conditions gave ketone **4** which was purified through recrystallization of its semicarbazide derivative **5**, leading to the pure compound in 65% overall yield. Finally, chiral imine **6** was obtained from reaction between ketone **4** and *R*-(+)-α-methylbenzylamine with azeotropic removal of water (Scheme 1).



Scheme 1.

It was assumed that reaction of imine **6** with *trans*-2-pentenone followed by hydrolysis of the imine and subsequent Robinson annulation could lead directly to (+)-α-vetivone **11**. However, preliminary results from our group have shown that *trans*-2-pentenone is not electrophilic enough to react at room temperature with an α-substituted imine and that when reactions are performed at temperatures above 60°C, only polymerisation of the *trans*-2-pentenone and hydrolysis of the imine are observed.[3] Consequently, we used an alternative pathway exploiting the high electrophilicity of phenyl crotonate which has already proved to be a valuable synthetic equivalent of *trans*-2-pentenone (Scheme 2).[1e,3,12,13]



Scheme 2.

Hence, reaction of crude imine **6** with phenyl crotonate afforded the Michael adducts which cyclized under the reaction conditions, leading to bicyclic lactam **7** and its isomers in 89% overall yield from ketone **4**. GC–MS analysis of the crude reaction mixture showed that besides the major compound **7**, a diastereoisomeric adduct (i.e. a priori *cis*-**7** or *trans*-**7**) and regioisomeric adducts of **7** are also formed (Fig. 1).

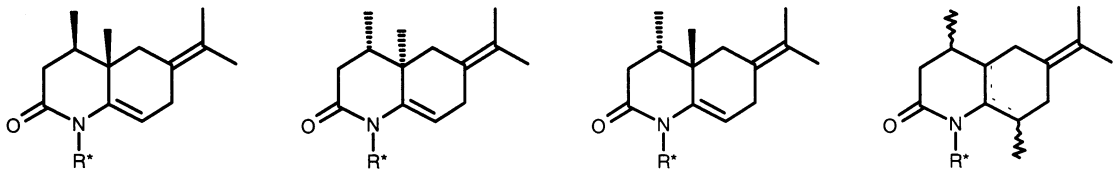


Figure 1.

In the usual situation, the mass spectra of stereoisomers are quasi-identical but differ from regioisomeric adducts.[14] This allowed us to determine the relative proportions of the two stereoisomeric adducts (97.5:2.5). The isomers are inseparable by flash chromatography and the structure of the minor component (*cis*-**7** or *trans*-**7**) was deduced after the next step. Thus, reductive cleavage of the chiral auxiliary R* afforded a mixture of lactam **8** and its isomers. GC–MS analysis of the crude reaction mixture revealed the presence of a single stereoisomer **8**, besides regioisomeric adducts. Flash chromatography allowed separation of the lactam **8** (47% yield from **4**, after recrystallization) from its regioisomers (41% yield from **4**). The relative configuration of the pure lactam **8** was determined from its ^{1}H NMR spectrum which shows that the H atom in the β-position of the carbonyl group has coupling constants of 13.0 Hz and 5.1 Hz (besides its coupling constant of 6.6 Hz with the methyl group) which are characteristic of a H atom in axial position. The relative configuration of lactam **8** is in accordance with the theoretical model obtained from an ab initio SCF-CI MO calculation study which has shown that Michael addition proceeds through a reactive complex with a chairlike compact structure (*syn* approach) having attractive secondary interactions between the C-atom of the carbonyl group of the electrophilic olefin and the N-atom of the imine, with a concerted proton transfer; thus, this chairlike structure allowed us to predict, with reactants bearing substituents, their stereochemical relationship in the adduct;[1b,c] these predictions were later confirmed experimentally.[1d,e,15]

The signal for the compound observed as 2.5% of the crude **7** mixture by GC–MS analysis has no equivalent in the analysis of crude **8** and therefore corresponds to stereoisomer *cis*-**7**.

These results show that the reaction is highly enantioselective (ee = 95%) and totally diastereoselective (>99%). One can note that a significant proportion of regioisomeric adducts was formed as it is usually observed when substituted electrophilic olefins are used in the Michael reaction of imines.[1d,e,12,13]

The synthesis of (+)-α-vetivone **11** was then achieved after three conventional steps which began with basic hydrolysis of lactam **8** (71% yield) followed by cyclization of the resulting ketoacid **9** to enol lactone **10** (63% yield). (+)-α-Vetivone **11** was finally obtained in 88% yield (8% yield from **1**) through a Belleau–Fujimoto type reaction using Corey's procedure.[16] The highly soluble compound was therefore purified through its semicarbazide derivative **12**. The data for pure target compound (+)-α-vetivone **11** are in full agreement with those reported in the literature, specially for the sign of the specific rotation, thus confirming the absolute configura-

tion depicted in Scheme 2. Once again, this absolute configuration is in accordance with that predicted from the heuristic rule elaborated previously.[1b]

This synthesis of (+)-α-vetivone also represents a formal synthesis of (+)-nootkatone since the racemic equivalent of the latter has been synthesised in two steps from (±)-α-vetivone.[8]

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded, respectively, at 300 MHz and 75.5 MHz ($CDCl_3$). Chemical shifts are reported in ppm (δ) relative to TMS. Thin-layer chromatography (TLC) was performed with aluminium plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualised under UV light and dipped in a Dragendorff solution. Silica gel (230–400 mesh) was used for flash chromatography (FC) separations and EtOAc/hexanes (% EtOAc given) was the eluent. Gas chromatography–mass spectrometry (GC–MS) was performed with a Hewlett–Packard 5890 GC apparatus (equipped with a 12 m×0.20 mm dimethylpolysiloxane capillary column) linked to a HP 5971 EIMS, at 140°C for 1 min, then 18°C/min up to 290°C. Melting points (mp) were determined with a Fisher–Johns apparatus. All reactions were performed under a nitrogen atmosphere. Unless indicated otherwise, organic phases were washed with a saturated NaCl aqueous solution, dried over $MgSO_4$, filtered, and evaporated under reduced pressure.

3.2. 8-Isopropylidene-1,4-dioxaspiro[4.5]decane **2**

Isopropyltriphenylphosphonium bromide[17] (28.1 g, 65.0 mmol) was added to NaH (60% in mineral oil, 1.85 g, 77.1 mmol) in dry DMSO (40 mL) at rt. The reaction mixture was stirred at 50°C until the appearance of a red colour; then, a solution of commercial 1,4-cyclohexanedione mono-ethylene ketal **1** (10.15 g, 65.1 mmol) in dry DMSO (40 mL) was added. After stirring for 16 h at 50°C the reaction mixture was cooled to rt and water (40 mL) was added. After ether extraction, the triphenylphosphine oxide was removed by filtration after precipitation from hexane. FC (10%+2% of triethylamine) afforded 9.10 g (77%) of oily compound **2**.

Compound **2**: EIMS m/z (rel. int.) 182 (M^+, 46), 167 (26), 153 (20), 123 (20), 99 (12), 95 (10), 86 (base); ^{1}H NMR 1.55–1.61 (m, 4H), 1.63 (br s, 6H), 2.20–2.29 (m, 4H), 3.90 (s, 4H); ^{13}C NMR 19.90 (2C), 26.60 (2C), 35.52 (2C), 64.01 (2C), 108.8, 121.5, 129.2.

3.3. 4-Isopropylidenecyclohexanone **3**

A 15% H_2SO_4 aqueous solution (3 mL) was added at rt to a mixture of silica gel (70–230 mesh, 17 g) and CH_2Cl_2 (50 mL). After 2 min, compound **2** (8.01 g, 44.0 mmol) was added and the reaction mixture was vigorously stirred at rt for 2 h. The silica gel was removed by filtration, washed with CH_2Cl_2 and the solvent evaporated to yield a residue which was purified by FC (10%, then 20%). Starting material **2** (0.92 g, 11%) was recovered and 4.60 g (85% yield calculated for a 89% conversion) of oily ketone **3** was obtained. An analytical sample of **3** was obtained by distillation.

Compound **3**: Bp 120°C (bath)/15 Torr; EIMS *m*/*z* (rel. int.) 138 (M^+, 77), 123 (12), 96 (34), 95 (29), 91 (10), 82 (19), 81 (base), 79 (24), 68 (23), 67 (52), 55 (22); IR (neat) 1710 cm^{-1}; ^1H NMR 1.71 (br s, 6H), 2.35–2.41 (m, 4H), 2.49–2.56 (m, 4H); ^{13}C NMR 20.08 (2C), 26.80 (2C), 40.19 (2C), 124.7, 126.0, 212.9.

3.4. 4-Isopropylidene-2-methylcyclohexanone **4**

To a solution of LDA [prepared by mixing 12.5 mL (89.1 mmol) of diisopropylamine and 33.3 mL (83.2 mmol) of BuLi (2.5 M hexanes) in anhydrous THF (40 mL) at −30°C and stirring for 30 min] was added dropwise, at −78°C, a solution of ketone **3** (8.20 g, 59.4 mmol) in anhydrous THF (20 mL). After 30 min, MeI (11.1 mL, 178 mmol) was added rapidly at −30°C. The mixture was then allowed to warm to rt, THF was evaporated under reduced pressure and water (40 mL) was added. After ether extraction, a GC–MS analysis of the resulting oily residue showed signals at 3.61 min (starting material **3**, 18%) and 4.06 min (ketone **4**, 82%). The residue was dissolved in a 50:50 mixture of ethanol/water (60 mL) and sodium acetate (7.30 g, 89.1 mmol) followed by semicarbazide hydrochloride (8.61 g, 77.2 mmol) were added to the reaction mixture at rt. After 1 h, a precipitate was isolated by filtration and recrystallization from ethanol afforded 8.05 g (38.5 mmol) of pure semicarbazide **5** as a white solid. Cyclohexane (70 mL) and aqueous 10% HCl solution (70 mL) were added to this compound at rt. The mixture was then vigorously stirred until total disappearance of the white solid. After 2 h, ether extraction and evaporation afforded 5.85 g (65% yield) of pure ketone **4** as a colourless oil.

Compound **5**: Mp 161–162°C (ethanol); IR (Nujol) 3460, 3180, 1690, 1575 cm^{-1}; ^1H NMR 1.11 (d, $J=6.2$ Hz, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 1.90–2.03 (m, 1H), 2.20–2.64 (m, 6H), 5.30 (br s, 1H), 6.10 (br s, 1H), 8.31 (s, 1H); ^{13}C NMR 16.82, 19.95 (2C), 25.53, 25.68, 36.23, 36.43, 124.1, 126.5, 156.0, 158.2.

Compound **4**: EIMS *m*/*z* (rel. int.) 152 (M^+, base), 137 (19), 123 (10), 110 (38), 109 (25), 95 (51), 82 (17), 81 (45), 67 (35); ^1H NMR 1.08 (d, $J=6.6$ Hz, 3H), 1.72 (s, 3H), 1.73 (s, 3H), 1.97–2.09 (m, 1H), 2.34–2.53 (m, 4H), 2.61–2.73 (m, 1H), 2.78 (dd, $J=5.5$, 14.3 Hz, 1H); ^{13}C NMR 14.80, 20.07, 20.12, 27.66, 35.97, 39.90, 43.89, 124.6, 126.2, 214.3.

*3.5. (4*R*,4a*S*)-4,4a-Dimethyl-6-isopropylidene-1-[1-(*R*)-phenylethyl)]-3,4,4a,5,6,7-hexahydroquinolin-2(1*H*)-one* **7**

A solution containing ketone **4** (3.60 g, 23.7 mmol) and (*R*)-(+)-α-methylbenzylamine (3.70 mL, 28.4 mmol) in toluene (45 mL) was heated under reflux in a Dean–Stark apparatus for 16 h. The toluene was then removed under reduced pressure giving the crude imine **6**. The compound was then reacted with phenyl crotonate[1e] (7.40 g, 45.7 mmol) in the presence of a trace of hydroquinone at 60°C for 7 days. GC–MS analysis showed signals at 7.87 min, 7.98 min, 8.06 min, 8.14 min, 8.29 min, 8.34 min, 8.45 min, 8.63 min (global 61%, regioisomers of **7**), 8.54 min (1%, diastereoisomer *cis* of **7**) and 8.74 min (38%, **7**). Ether (60 mL) and 2.5 M NaOH aqueous solution (25 mL) were then added at rt and the reaction mixture was stirred for 30 min. Ether extraction followed by FC (10% then 20%) afforded 6.80 g (89% overall yield from **4**) of a mixture of lactam **7** and its isomers as an oil.

Compound **6**: EIMS *m*/*z* (rel. int.) 255 (M^+, 21%), 106 (10), 105 (base), 79 (11), 77 (11); IR (neat) 1650 cm^{-1}.

Coumpound **7**: EIMS *m*/*z* (rel. int.) 323 (M^+, 24%), 219 (36), 205 (16), 204 (base), 105 (55), 77 (21).

3.6. (4R,4aS)-(–)-4,4a-Dimethyl-6-isopropylidene-3,4,4a,5,6,7-hexahydroquinolin-2(1H)-one **8**

A solution of the above mixture of lactam **7** and its isomers (2.80 g, 8.67 mmol) in anhydrous THF (70 mL) was added to liquid NH_3 (140 mL) at −78°C. Lithium (0.70 g, 100 mmol) in small pieces was then added at the same temperature. After 1 h, the excess lithium was destroyed with a few drops of styrene, NH_3 was evaporated at rt and water (60 mL) was added. After ether extraction, the crude mixture was analysed by GC–MS showing a mixture of non-resolved regioisomers of **8** (4.74 min, 56%) and lactam **8** (5.39 min, 44%). Separation by FC (50% then 60%) followed by recrystallization from a mixture of AcOEt/hexane gave 1.00 g (47% yield from **4**) of **8** and 0.87 g (41% yield from **4**) of regioisomers of **8**.

Compound **8**: Mp 200°C (AcOEt/hexane); $[\alpha]_D^{20}$ −212 (*c* 0.9, EtOH); EIMS *m*/*z* (rel. int.) 219 (M^+, 54%), 205 (15), 204 (base), 162 (17), 134 (25), 108 (11); IR (Nujol) 3170, 1660 cm^{-1}; ^1H NMR 0.89 (s, 3H), 0.98 (d, $J=6.6$ Hz, 3H), 1.68–1.76 (m, 7H), 1.89 (ddq, $J=5$, 6, 13 Hz, 1H), 2.23 (dd, $J=12.9$, 18.0 Hz, 1H), 2.41 (dd, $J=5.1$, 18.0 Hz, 1H), 2.59–2.71 (m, 1H), 2.76 (d, $J=13.6$ Hz, 1H), 3.02 (dd, $J=4.4$, 20.2 Hz, 1H), 4.83 (dd, $J=3.3$, 4.4 Hz, 1H), 7.65 (br s, 1H); ^{13}C NMR 14.04, 15.15, 19.83, 20.16, 27.98, 35.55, 36.47, 36.74, 38.05, 102.9, 124.3, 124.8, 140.4, 170.0; HRMS: calcd for $C_{14}H_{21}NO$ (M^+): 219.1623, found: 219.1626.

Regioisomers of **8**: EIMS *m*/*z* (rel. int.) 219 (M^+, 46%), 205 (15), 204 (base), 176 (15), 162 (17), 134 (14).

3.7. (3R,1S)-(–)-3-(5-Isopropylidene-1-methyl-2-oxocyclohexyl)butyric acid **9**

To lactam **8** (0.85 g, 3.88 mmol) dissolved in ethanol (15 mL) was added a solution of KOH (2.60 g, 46.6 mmol) in ethanol (15 mL). The reaction mixture was flushed with argon and heated at 80°C for 48 h. After removal of the ethanol under reduced pressure, a 10% HCl aqueous solution was added up to pH 1. After ether extraction, FC (30% then 50%) followed by recrystallization from a mixture of AcOEt/cyclohexane (30:70) gave 0.66 g (71%) of ketoacid **9** as a white solid.

Compound **9**: Mp 141°C (AcOEt/cyclohexane); $[\alpha]_D^{20}$ −49.5 (*c* 1.4, EtOH); EIMS *m*/*z* (rel. int.) 238 (M^+, 2%), 222 (51), 163 (14), 162 (19), 151 (27), 135 (96), 107 (base), 93 (78), 91 (27), 79 (30), 77 (21), 67 (37), 55 (34), 53 (23); IR (Nujol) 1717 cm^{-1}; ^1H NMR 0.91 (s, 3H), 0.95 (d, $J=6.6$ Hz, 3H), 1.71 (s, 3H), 1.73 (s, 3H), 1.80–2.80 (m, 9H), 10.80 (br s, 1H); ^{13}C NMR 14.41, 17.58, 20.20, 20.29, 28.06, 33.80, 36.64, 37.61, 38.54, 51.43, 124.1, 126.5, 179.1, 216.5; HRMS: calcd for $C_{14}H_{22}O_3$ (M^+): 238.1569, found: 238.1566.

3.8. (4R,4aS)-(–)-4,4a-Dimethyl-6-isopropylidene-3,4,4a,5,6,7-hexahydrochromen-2-one **10**

A solution of ketoacid **9** (0.60 g, 2.52 mmol) and AcONa (20 mg) in Ac_2O (20 mL) was heated under reflux for 3 h. After evaporation of the Ac_2O under reduced pressure, and ether extraction, the organic layer was washed with an aqueous Na_2CO_3 solution before the usual work-up. FC (10% then 30%) followed by recrystallization from cyclohexane yielded 0.345 g (63%) of lactone **10** as a white solid.

Compound **10**: Mp 79°C (cyclohexane); $[\alpha]_D^{20}$ −137 (*c* 2.8, EtOH); EIMS *m*/*z* (rel. int.) 220 (M^+, 40%), 151 (28), 150 (15), 149 (13), 135 (32), 121 (17), 109 (base), 107 (27), 91 (25), 79 (23), 77 (23), 69 (54), 55 (26); IR (Nujol) 1750 cm^{-1}; ^1H NMR 0.85 (d, $J=0.7$ Hz, 3H), 0.90 (d, $J=6.6$ Hz, 3H), 1.64 (br s, 6H), 1.71 (d, $J=13.2$ Hz, 1H), 1.89 (ddq, $J=7$, 7, 13 Hz, 1H), 2.28 (dd, $J=12.9$, 18.4 Hz, 1H), 2.57 (dd, $J=5.5$, 18.8 Hz, 1H), 2.52–2.62 (m, 1H), 2.69 (dd, $J=1.5$, 13.2 Hz, 1H), 2.96 (dd, $J=4.4$, 19.5 Hz, 1H), 5.15 (dd, $J=3.4$, 4.8 Hz, 1H); ^{13}C NMR 13.88, 14.87, 19.98, 20.27, 27.55, 34.84, 35.34, 36.66, 38.67, 104.7, 123.2, 125.7, 154.8, 167.7; HRMS: calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463, found: 220.1464.

*3.9. (4*R*,4a*S*)-(+)-4,4a-Dimethyl-6-isopropylidene-4,4a,5,6,7,8-hexahydro-(3*H*)-naphthalen-2-one, (+)-α-vetivone **11***

n-BuLi (2.5 M in hexanes, 1.09 mL, 2.73 mmol) was slowly added at −78°C to a solution of $CH_3P(O)(OMe)_2$ (0.37 mL, 3.34 mmol) in anhydrous THF (10 mL). After 5 min, a solution of lactone **10** (0.30 g, 1.36 mmol) in anhydrous THF (2.5 mL) was added and the temperature was raised to −20°C for 3 h. Water (10 mL) was then added and an ether extraction followed by FC (20%) gave 0.26 g (88%) of (+)-α-vetivone **11** as a solid. The compound was purified through its semicarbazide derivative since its high solubility and low melting point prevent its easy recrystallization. Thus, (+)-α-vetivone **11** (0.22 g, 1.01 mmol) was dissolved in ethanol (2 mL) and water (2 mL); sodium actetate (0.21 g, 2.61 mmol) was added, followed by semicarbazide hydrochloride (0.25 g, 2.26 mmol). After 1 h, the resulting precipitate was isolated by filtration and recrystallization of this material from ethanol afforded 0.18 g (0.68 mmol) of pure semicarbazide **12** as a white solid, mp 240°C [lit.[18] 222–223°C]. The compound was then vigorously stirred in a mixture of cyclohexane (10 mL) and 20% HCl aqueous solution (10 mL), at 50°C. After 2 h, ether extraction afforded 0.115 g (52% yield from crude **11**) of pure (+)-α-vetivone **11** as a colourless solid.

Compound **11**: Mp 50–51°C [lit.[18] 51–51.5°C, pentane; lit.[5b] 50–51°C, light pet.]; $[\alpha]_D^{20}$ +219 (*c* 0.5, EtOH) [lit.[19] +234 (*c* 8.0, EtOH); lit.[5b] +225 (*c* 4.91, EtOH)]; EIMS *m*/*z* (rel. int.) 218 (M^+, 52%), 203 (21), 186 (14), 185 (base), 161 (22), 157 (11), 147 (22), 121 (19), 105 (15), 91 (19) [lit.[8,20] similar]; IR (Nujol) 1665, 1615 cm^{-1} [lit.[6] (film) 1669, 1621 cm^{-1}]; ^1H NMR 0.98 (s, 3H), 1.02 (d, $J=6.6$ Hz, 3H), 1.63–1.75 (m, 1H), 1.73 (br s, 3H), 1.74 (br s, 3H), 1.80–2.50 (m, 6H), 2.70–2.85 (m, 2H), 5.77 (d, $J=1.5$ Hz, 1H) [lit.[6] (CCl_4/C_5H_5N) similar; lit.[5b] similar]. ^{13}C NMR 15.02, 16.30, 20.01, 20.05, 29.81, 33.63, 39.10, 40.67, 41.61, 42.21, 124.1, 124.6, 126.7, 171.5, 199.5; HRMS: calcd for $C_{15}H_{22}O$ (M^+): 218.1671, found: 218.1675.

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